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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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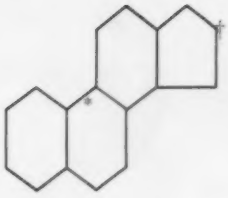

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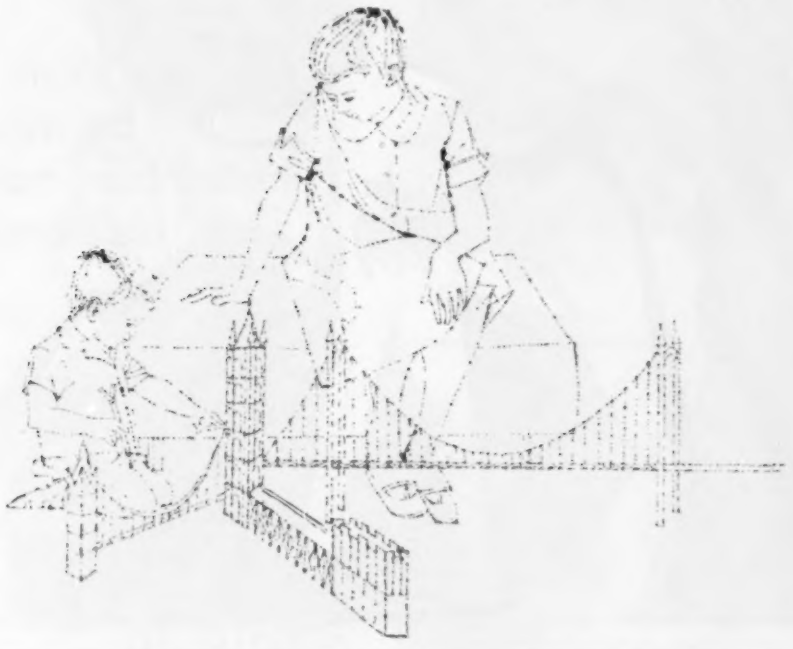

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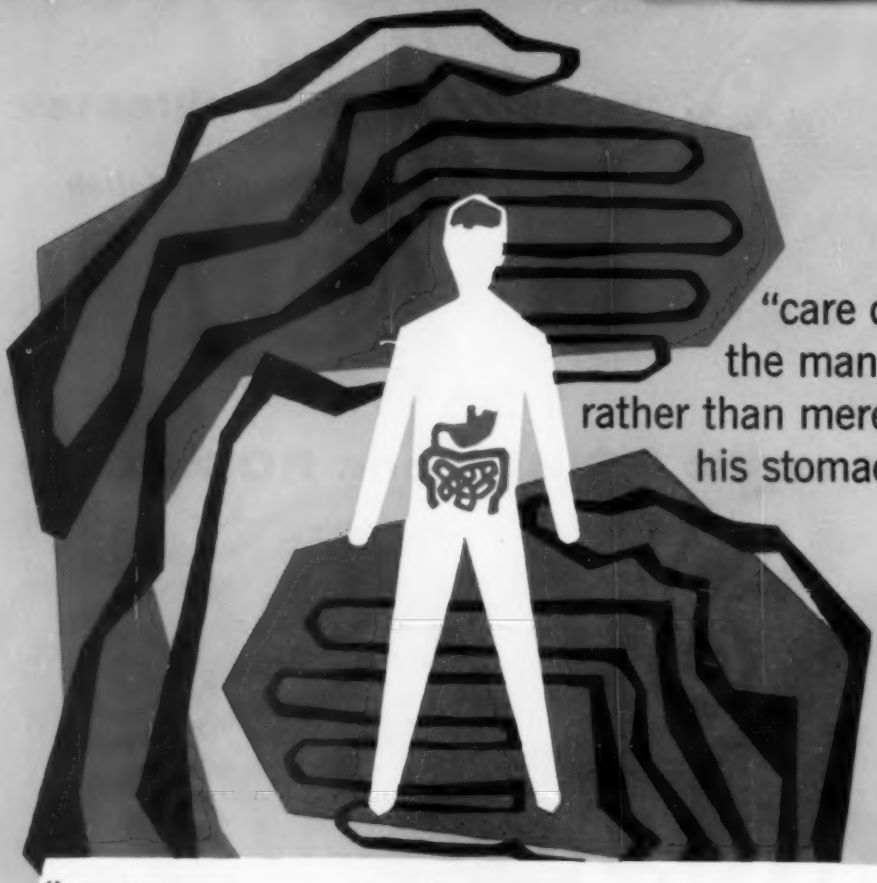

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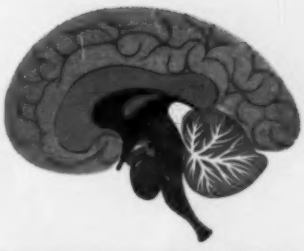

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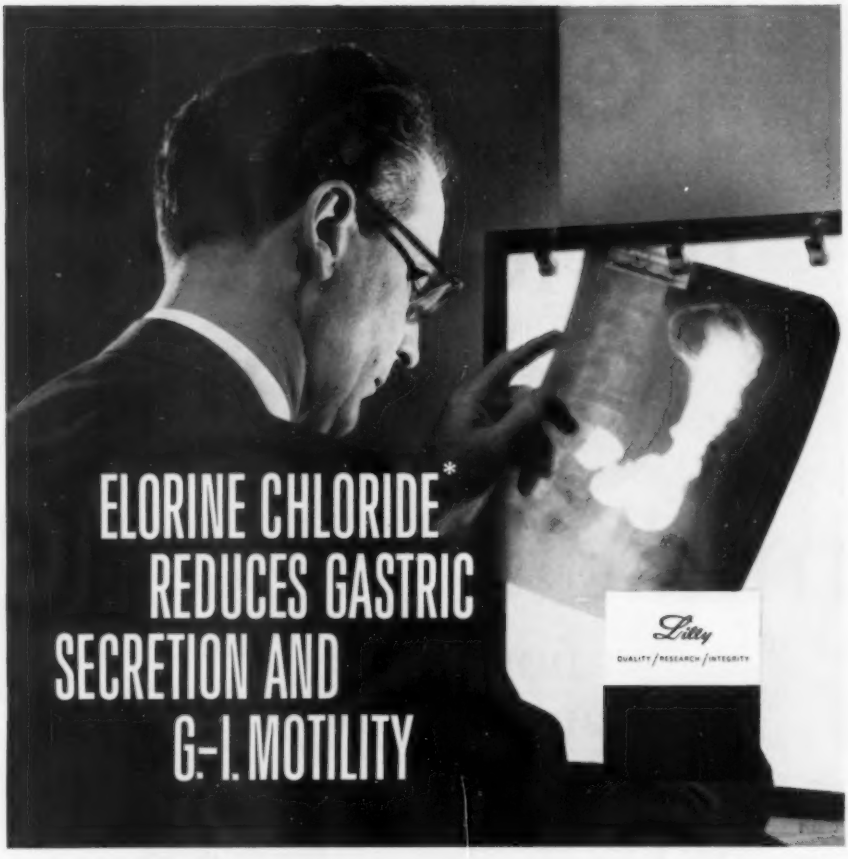

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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

CONTENTS

The Modern Aspects of the Diabetic Problem . . . 73
Garfield G. Duncan

Use of the Electron Microscope in the Study of Intracellular Virus 85
Councilman Morgan, Harry M. Rose and Dan H. Moore

Study of Alcoholism with Onset Forty-Five Years or Older 99
Harry H. Moorhead

Therapy of Infections 109
Transcription of a Panel Meeting
David E. Rogers, Aaron D. Chaves, Edwin D. Kilbourne, Ralph R. Tompsett and Theodore E. Woodward

New York Pathological Society: Abstracts 134

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 34, NO. 2 FEBRUARY 1958

THE MODERN ASPECTS OF THE DIABETIC PROBLEM*

The Ludwig Kast Lecture†

GARFIELD G. DUNCAN

Professor of Medicine, University of Pennsylvania;
Director, Medical Divisions, Pennsylvania Hospital and the Benjamin Franklin Clinic,
Philadelphia, Pennsylvania

IT is a privilege and an honor to participate in your Postgraduate Week and especially to join with you in honoring Dr. Ludwig Kast, for whom this lecture was named and from whose proposal this great educational enterprise of yours has developed.

Basic concepts and fundamentals in the treatment of diabetes remain relatively constant. Only minute fragments of the enormous amount of investigation in this field become integrated into the permanent fabric of our understanding and into the clinical management of this disorder. The scanning of the accomplishments of investigators and the selection of the fruits of their endeavors that hold promise in clinical application are not always as simple as their formal appearance, reduced to a few sentences in a standard text, might infer.

I shall avail myself of the latitude permitted in the title of this

* Presented at the Postgraduate Week, replacing the *Graduate Fortnight* of former years, of The New York Academy of Medicine, October 8, 1957.
† In honor of Dr. Ludwig Kast who first suggested the Graduate Fortnight.

paper by dealing with what I consider to be some of the problems which are in varying stages of solution.

Classification

It takes courage to come to grips with the problem of classifying diabetes. However, as components of the puzzle have fallen into place, a reasonable classification has evolved. Grades of severity of diabetes may alter as the variety of influences to which these patients are subject assert themselves. The diabetes may recede so far into the background that it is not detectable in some obese patients who reduce adequately their total caloric intake; others may be neglectful and experience unfavorable progression of the disorder. The diabetes in one patient may be classified differently at different times, for example, the obese patient who because of neglect, or ignorance, may lose weight because of the degree of glycosuria. When he becomes underweight under these influences he has increased his sensitivity to insulin; he is more prone to ketosis than he formerly was and his diabetes is much less stable than it had been. This transition from one phase of the disorder into another does not alter the practicability of the classification (Table I) if it is used in the light of good clinical judgment.

Primary or essential diabetes, because of its great frequency, our inability, not knowing its cause, to do more than reduce predisposing influences, and its proclivity for causing progressive degenerative disorders, presents a major clinical problem.

It is significant that ketosis, progressive degenerative changes and an apparent hereditary influence, as occur characteristically in primary diabetes, are not features of secondary diabetes. Furthermore, secondary diabetes is curable if the cause is identified and if it is practicable to remove it, for example, removal of a corticoid tumor.

The Enigma of the Prediabetic State

Probably all who have cared for many diabetic patients have had occasion to observe some of the characteristics of diabetes in individuals who lacked any detectable evidences of disturbed carbohydrate metabolism. Even the response to the glucose tolerance test has been normal. But, after some years have elapsed hyperglycemia and glycosuria appear. A common indication of a prediabetic state

TABLE I—A CLINICAL CLASSIFICATION OF DIABETES MELLITUS

I. Primary, or essential, diabetes—adult type
   A. *Relatively stable*
      Onset in adult life
      Overweight is usual (80% +)
      Relatively insensitive to insulin
      Not prone to develop ketosis, in the absence of acute complications
   B. *Unstable*—juvenile type
      Onset usually in childhood or youth
      Very sensitive to insulin
      Very susceptible to ketosis

II. Secondary diabetes
   A. Hyperadrenalism
      1. Cortical—Cushing's syndrome and primary aldosteronism
         —corticoid therapy
      2. Medullary—pheochromocytoma
   B. Hyperpituitarism
      1. Acromegaly
      2. Pituitary basophilism
      3. Therapy—adrenicotrophic (ACTH) and growth hormones
   C. Hyperthyroidism (rarely, if ever, a cause of clinical diabetes)
      1. Thyrotoxicosis
      2. Thyroid therapy
   D. Destruction or excision of islet tissue
      1. Hemochromatosis
      2. Pancreatitis
      3. Cystic disease or neoplasm of pancreas
      4. Removal of pancreas
      5. Trauma to pancreas (?)

is seen in women who give birth to large babies. The prediction that *the mother of an infant weighing more than 10 pounds* at birth will ultimately develop clinical diabetes is more likely than not to be fulfilled. This result is especially likely if the mother has diabetic relatives.

The *glucose tolerance test* as ordinarily employed is of value in detecting pre-clinical diabetes *in pregnant subjects* between the end of the fourth month and the termination of the pregnancy. The hyperglycemic response subsides after delivery. Hoet[1] attributes this abnormality, most frequent in patients with a family history of diabetes, to hypercorticism and its effect upon the islands of Langerhans.

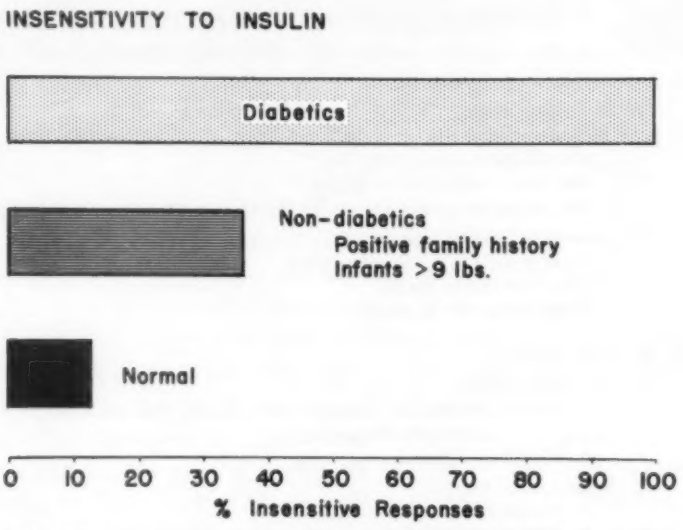

Fig. 1. Glucagon-free insulin sensitivity tests indicate that all adult diabetics' tests showed relative insensitivity to insulin. Thirty-eight per cent of non-diabetic women who had a family history of diabetes and who had given birth to infants weighing more than 9 pounds were relatively insensitive to insulin in contrast to 12.5 per cent of presumably normal men and women.

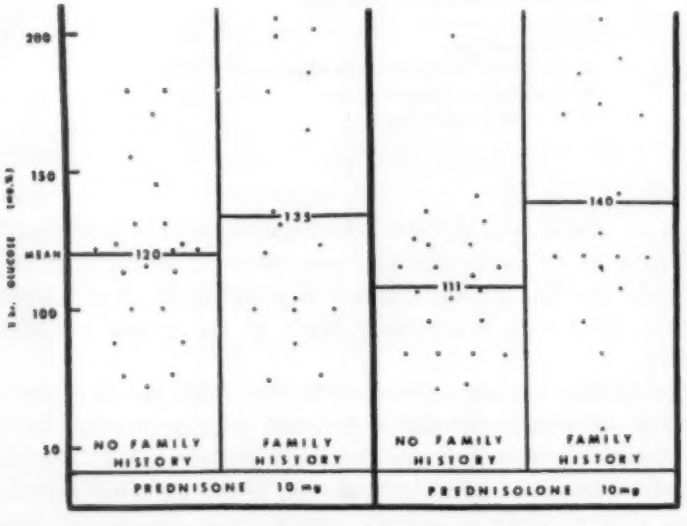

Fig. 2. Results of steroid-glucose tolerance tests (Somogyi-Nelson). A family history of diabetes reflects unfavorably in this test when either prednisone or prednisolone was given prior to the ingestion of the glucose. Reprinted by permission of K. M. West and American Diabetes Association, ref. 5.

Furthermore, he believes that correction of this disturbance in carbohydrate metabolism, by giving insulin, will reduce fetal mortality. Time will tell whether or not the appearance of diabetes in the mother later in life will in this manner also be prevented.

Detection of a *relative insensitivity to insulin* may indicate a prediabetic state. This has been suggested by Anderson's observations[2] and by a survey made by Drs. K. Young, C. F. Lee and G. Schless[3] at the Pennsylvania Hospital. Women who had less than a 10 per cent reduction in the blood sugar level within ten minutes after the intravenous administration of 3 units of glucagon-free crystalline insulin are considered to be relatively insensitive to insulin. All adult diabetics were found, by this modified Anderson[2] test,* to be relatively insensitive to insulin, as were 36 per cent of nondiabetic women who had a family history of diabetes and who had borne infants weighing more than 9 pounds. Of the women, 29 in number, who had babies weighing more than 9 pounds but who had no family history of diabetes, 38 per cent were unusually insensitive to insulin. In contrast, only 12.5 per cent of presumably entirely normal women and men showed relative insensitivity to insulin (Fig. 1).

Functional burdens on the pancreatic islets may expose reduced reserve capacity to deal with carbohydrate long before clinical diabetes is manifest. In the adult, a blood sugar value in excess of 130 mg. per cent (Folin-Wu) two hours *after the ingestion of 100 gm. of glucose* in the fasting state is presumptive evidence of an early diabetes. This is an effective screening test for relatives of diabetics. However, this test may reveal no abnormality. Functional stress may be further magnified, as suggested by Fajans and Conn[4] and by West.[5] The *glucose tolerance test is modified by giving a steroid* eight and one half hours before the oral administration of glucose. Prednisone or prednisolone exerts greater hyperglycemic effects than cortisone acetate or hydrocortisone.[5] The true glucose values obtained by the Somogyi-Nelson method were determined two hours after the ingestion of glucose. The interpretation that abnormally high blood sugar values indicate a prediabetic state may be considered speculative but the significant increase in the incidence of high values in relatives of diabetics as compared with those who had no diabetic relatives is supporting evidence. The results reported by West[5] are shown in

* This test involves giving 3 units of glucagon-free crystalline insulin intravenously to a patient in the fasting state and taking blood samples at two minute intervals for ten minutes.

Figure 2. These support the studies of Fajans and Conn[4] which indicated that 24 per cent of the subjects with a positive family history showed substantially abnormal glucose tolerance curves after receiving cortisone. Only 3 per cent of subjects having no family history of diabetes showed similar impairment as indicated by the cortisone-glucose tolerance tests.

Other, but uncommon, stigmata of the prediabetic state are *retinal changes* and *neuropathies*, both being indistinguishable from those seen in fully developed diabetes. *Mild degrees of hypoglycemia* have been reported as being an early clinical indication of diabetes.[6] These criteria of pre and early diabetes are more likely to be missed than is the case of the mother of an 11 pound baby.

Obesity affecting members of diabetic families is so common and so frequently a forerunner of diabetes that one is justified in considering it as inseparable from the unknown processes which prevail in the prediabetic state in adults. Unlike the prediabetic retinal and neuropathic changes, obesity is also a precipitating factor. The ease with which diabetes is controlled by the therapeutic reduction in weight of the obese diabetic is presumptive evidence that the prevention or correction of obesity in members of diabetic families may prevent the development of clinical diabetes.

Until the enigma of the prediabetic is solved, the foregoing means of its detection serve as indications for measures aimed to prevent clinical diabetes. The measures at hand that may serve this purpose, as well as control mild forms of diabetes, are: the avoidance of overeating, the correction of obesity, and control with diet and insulin of the disturbance in carbohydrate metabolism during pregnancy and during other episodes which may be accompanied by what appears to be a transitory diabetes, for example, carbuncles. These measures and a suitable regimen of daily exercise offer some prospects for the prevention of diabetes.

The Overweight Diabetic

Approximately 82 per cent of adult diabetics are overweight when they seek treatment. Too little effort is made to reduce the weights of these patients and resort to insulin or tolbutamide is adopted too readily. This is the easy way, but it permits the patient to remain overweight in most instances. A study of the composite experience of

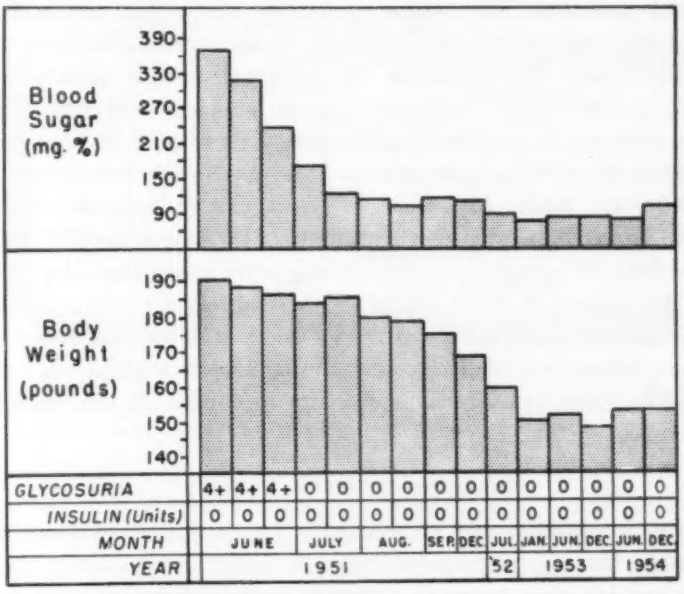

Fig. 3. Typical effect of therapeutic undernutrition in obese diabetics. The clearing of glycosuria and the correction of the hyperglycemia are associated with the reduced diet and the decrease in body weight.

insurance companies of the effect of overweight on longevity, and especially as it applies to diabetic patients, is enlightening. Overweight diabetics have a mortality rate 2.5 times that of normal, but if the degree of overweight exceeds 25 per cent, the mortality is eight times that normally expected.

The effective reduction of the obese diabetic involves a well-planned campaign that may of necessity be lifelong. The obese diabetic should not intensify his or her appetite by excessive physical exercise or by insulin therapy. Fortunately, tolbutamide does not increase the appetite. However, if it is employed in the treatment of the obese diabetic, diet therapy will be given little credit and less heed by all but the exceptional patient.

Reduction of the caloric intake, invoking the principles established some forty years ago by Dr. Frederick M. Allen, remains the treatment of choice for these patients. If prescribed and if adhered to, the weight reduction diet will suffice without drug therapy in the majority

of adult diabetics. The degree of success will reflect the zeal and confidence with which the treatment is instituted. The control of glycosuria and hyperglycemia by undernutrition is illustrated in Figure 3. The weight reduction regimen supplemented with appropriate amounts of vitamins is a temporary measure, following which additions to the diet adequate to maintain a satisfactory state of nutrition are made. My diabetics' diets closely approach that of normal individuals after undernutrition is no longer needed. Severe restrictions are unnecessary, but the respective meals from day to day must be uniform if good control of the diabetes is to be maintained. The evidence that good control should be achieved and maintained is overwhelming. All will agree that during acute complications, insulin should be given to overweight diabetics to counteract the tendencies to ketosis at such times.

Selection of Drug Therapy

Dietary considerations are necessary for all diabetic patients. *Tolbutamide therapy* is probably next in order of frequency in the treatment for new cases of uncomplicated diabetes. It is a treatment of convenience not requiring injections. All diabetic patients who developed diabetes after 40 years of age, who are not appreciably overweight, who have no acute complications, and who would formerly have *required insulin to control the diabetes* are proper candidates for trial therapy with tolbutamide. For those who are overweight, tolbutamide therapy may be given advantageously, but this should be considered a temporary measure and one to be discontinued when a suitable reduction in weight achieves control of the diabetes without it. Substitution of tolbutamide therapy for correction of obesity will probably be widespread. This practice is to be deprecated.

In more than two-thirds of the patients referred to, the diabetes will respond adequately to tolbutamide, which is ineffective when the diabetes has developed in youth. Also, it is ineffective in the presence of acute febrile complications and with rare exceptions in patients who develop ketonuria readily, hence the need for adequate training in insulin therapy as, sooner or later, the diabetic, as is the case in the nondiabetic will have acute complications to contend with.

In considering *tolbutamide* (Orinase) *therapy*, patients who have developed diabetes in childhood or youth may be excluded. For the

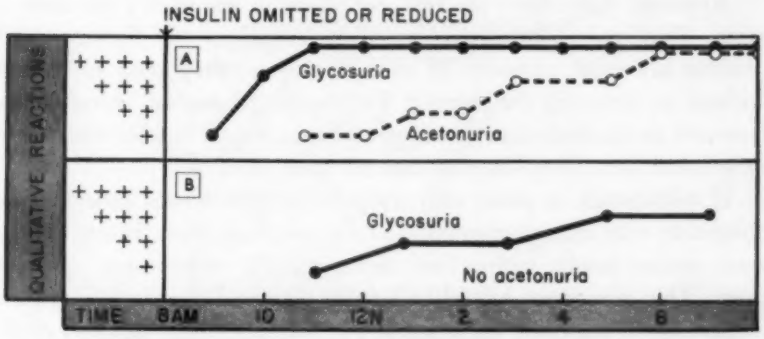

Fig. 4. Predicting the effects of tolbutamide. Patient A: Increasing glycosuria and acetonuria following the omission or appreciable reduction of insulin indicate that, in all likelihood, tolbutamide will not be effective. Patient B: Glycosuria but no acetonuria is presumptive evidence that tolbutamide therapy will be effective.

"adult acquired diabetes" it is a good plan to be sure that the patient needs drug therapy before embarking on a treatment that may not be necessary. Even specialists in the treatment of diabetes have been surprised to find that in many of their patients past middle age no glycosuria nor hyperglycemia followed the withdrawal of insulin. But in those cases in which insulin is actually needed, it may be abruptly withdrawn when the requirement does not exceed 20 units daily. If glycosuria occurs in increasing amounts, a trial of tolbutamide therapy is justified. Prompt control of the glycosuria will be proof of its effectiveness. If the insulin dosage exceeds 20 units, the amount given may be reduced by one-half for the first and omitted on the second day if no glycosuria occurs.

The prompt appearance of ketonuria, and in increasing amounts, during the first twelve hours indicates that no benefit need to be expected from tolbutamide and that insulin therapy should be promptly resumed if unfavorable progression of the ketosis is to be avoided. An instance of these findings is depicted in Figure 4 (Patient A).

On the other hand, if no ketonuria appears when insulin is discontinued, as in the case of Patient B (Fig. 4), it is highly probable that tolbutamide therapy will be adequate to control the diabetes.

Hypoglycemia, in our experience, is an uncommon complication of this therapy. Possibly this is because we do not give more than 1.5 gm. daily and more often less than this amount.

Apparent side effects are few, occurring in less than 3 per cent of cases. Skin rashes–urticarial, macular, eruptions or flushing–with pruritus are most common. If of mild degree, they tend to subside without interrupting the therapy. Leukopenia, disturbed bromsulfalein tests and elevated alkaline serum phosphatase values in mild and transitory forms have been observed but are quite rare.

If tolbutamide is given only to patients who would otherwise be obliged to take insulin, approximately 33 per cent must, in my experience, resume insulin within four to ten months without any apparent cause. This experience would be largely obscured if one yields to the temptation to prescribe tolbutamide for patients whose diabetes could be controlled by diet therapy alone.

Though many thousands of patients have taken tolbutamide for many months without apparent harm, it would be well to consider it as still on trial until time has shown it to maintain its effectiveness without untoward effects indefinitely.

Insulin is the ideal physiological agent. Because of the inconvenience of its administration, however, its use will probably be increasingly restricted to those patients whose diabetes cannot be controlled by diet alone, or with, oral therapy.

Insulin therapy is imperative in all juvenile diabetics and in all adults who acquired diabetes in youth and in those who develop ketonuria abruptly and in increasing amounts following the omission, or an appreciable reduction, of insulin.

Insulin is essential in the treatment of diabetes during acute infections, ketosis and surgery, and it is equally essential for the pregnant diabetic.

The selection of the appropriate insulin therapy is complicated by the fact that there are six insulins commercially available in this country, and if one writes for an international audience the number is increased to eight by including the rapidly acting amorphous insulin zinc suspension (semi-lente) and a long acting crystalline insulin zinc suspension (ultra-lente). There are three *rapidly acting insulins*–regular, crystalline and semi-lente; three *intermediate acting insulins*–globin, isophane (NPH) and lente; and two *long acting insulins*–protamine zinc and ultra-lente.

Some diabetics do well with a single dose of an intermediate acting *insulin* (globin, isophane [NPH] or lente) one hour before breakfast.

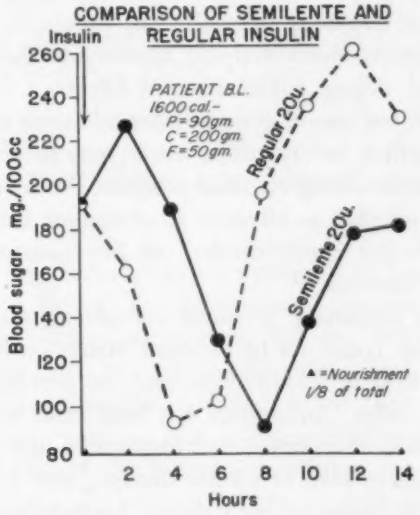

Fig. 5. The speed of action, the degree and duration of effect of semi-lente insulin compared with those of regular insulin. Identical amounts of nourishment were given in liquid form at two-hour intervals.

Others require the addition of crystalline insulin—rapidly acting—to an intermediate insulin—in my experience NPH is preferable. For the control of unstable diabetes, this mixture given one half hour before breakfast and a small amount of NPH insulin after supper or at bedtime has served us best. The total amount needed may be tried as a 2:1 mixture of crystalline and protamine zinc insulins given before breakfast. The efficiency of this plan of therapy is occasionally so good it is worth a trial. Mixtures of semi-lente and ultra-lente insulins, titrated to the needs of the individual, promise to increase considerably the number of patients who will achieve good control by one daily injection.

It was hoped that the "lente family of insulins" would cover the needs of all diabetics requiring insulin. That this is not the case is indicated in Figure 5. Regular insulin is shown to reduce the blood sugar more rapidly than the rapidly acting amorphous insulin zinc suspension (semi-lente) insulin, hence is the insulin of choice when greatest possible speed of action is desired. The method of comparing the effects of these two insulins, as shown in Figure 5, has proven to be most effective.

The day's diet is prepared in liquid form, and equal fractions of the total are given at two-hour intervals. The metabolic burden of these closely placed nourishments sharpens appreciably the appraisal of the contrast of speed, degree and duration of effect.

During acute, but minor, complications additions to the usual doses of insulin may suffice, or crystalline insulin may be given at four hour intervals without disturbing the usual program. For severe complications we have found no plan so effective as crystalline insulin given every six hours with the diet equally divided into four nourishments and given also at six hour intervals.[7, 8]

Some of the perplexing problems concerning diabetes have been touched on. Many could not be included. Attention has been directed to the prediabetic state, its detection, and the potential advantages its recognition may offer. An attempt has been made to place diet, tolbutamide and insulin therapies in their appropriate and respective places, and a comprehensive plan of insulin therapy, that lends itself to the substitution of the insulin of one's choice, has been submitted.

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USE OF THE ELECTRON MICROSCOPE IN THE STUDY OF INTRACELLULAR VIRUS*†

COUNCILMAN MORGAN, HARRY M. ROSE and DAN H. MOORE

NEARLY twenty years have passed since Kausche, Pfankuch and Ruska[1] first demonstrated tobacco mosaic virus in the electron microscope. Not until five years ago, however, did detailed visualization of viruses within cells become feasible. Although examination of thin sections at high resolution constitutes a new and important method of studying viruses, the acquisition of data is, and will continue to be, a slow process beset with difficulties. To understand the contribution that electron microscopy is making, to appreciate the nature of its limitations and to perceive the role it may play in the immediate future requires some knowledge of the instrument and the techniques currently employed.

The electron microscope is essentially an evacuated tube several feet long containing three magnetic lenses and a series of small apertures. Electrons are emitted from a tungsten filament at one end and are accelerated by a strongly charged (50,000-100,000 volts) positive field. As they pass down the column their direction is controlled by the magnetic fields of the lenses. Upon striking the specimen, which is inserted near the half-way mark, electrons are scattered by dense structures but continue with little deflection through areas of low density. A fluorescent plate viewed through lead glass windows near the end of the tube translates the energy of the electrons into light and thus permits the image of the section to be seen. A micrograph is obtained by flipping the fluorescent plate to one side and exposing a photographic plate immediately beneath.

The electron microscope provides but one advantage over the light

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microscope, namely, higher resolution (10-20Å)* and consequently greater magnification (over 100,000 x). There are several important disadvantages. First, the specimen must be placed in a vacuum and therefore dehydrated. Second, electrons are easily deflected and hence the specimen (as in the case of sections) must be extremely thin. Third, the electrons excite heat in any object they strike. The actual temperature of specimens during examination has not been recorded, but it is sufficient to alter their appearance.[2] Fourth, since electrons cannot impart color, the selective staining which is so helpful to the light microscopist cannot be achieved. Fifth, the size of the field is inversely proportional to the degree of magnification and, consequently, at the magnification necessary to reveal details of viral structure, only a very small part of the host cell can be viewed on the photographic plate.

Until recently the morphologic study of viruses has been largely confined to the examination of dried down suspensions. Since electrons can penetrate a virus only to a limited extent, the image obtained was generally a silhouette which revealed size and shape but little internal structure. Even size and shape were frequently distorted by the surface forces which accompany the process of desiccation. New impetus was given to electron microscopy by the observation that a plastic—methacrylate—was a satisfactory embedding substance, preserving tissue structure and being easily sectioned.[3] The tobacco mosaic virus was the first to be seen intracellularly,[4] followed by fowl pox,[5] influenza[6] and vaccinia.[7,8] These early specimens, cut on modified standard microtomes, were too thick to permit detailed examination of viral structure. With the development of special microtomes, however, ultra-thin sections could be obtained which allowed high resolution micrography, and shortly thereafter the recognition of osmium tetroxide as a suitable fixative[9] permitted study of viral and cellular morphology in a relatively good state of preservation.

At present tissues are generally fixed in buffered, isotonic osmium tetroxide, dehydrated in graded concentrations of alcohol and embedded in liquid methacrylate, which is polymerized by heat (40-60°C.) or ultraviolet radiation. The sections are cut on microtomes equipped with glass, polished steel or diamond knives and placed on metal grids covered with a supporting film. Although it is difficult to measure accurately the thickness of the sections, they probably average about

* 1 mm. = 1,000,000 mu = 10,000,000 Å

30-40 mμ.[10] Such specimens provide but two advantages over those employed for light microscopy: they allow passage of electrons and minimize superimposition of structure. There are several disadvantages associated with the above preparatory methods. First, penetration of osmium tetroxide into tissues is slow and the proper fixation of large blocks is difficult. Second, polymerization of methacrylate may not be uniform, resulting in variable, and often severe, damage to fine structure. Third, the sections reveal in depth ca. 1/100 of what we are accustomed to see in the light microscope. Fourth, only a very small face (averaging 0.3 x 0.5 mm.) can be cut from the block. Fifth, approximately 30 per cent of any given section is hidden beneath the wire of the supporting metal grid. If to these disadvantages we add the fact that multiple scanning micrographs must be taken because the image on the fluorescent plate is deficient in resolution and contrast, it should be evident why data accumulate slowly. Under such circumstances the mere recognition of a virus amid the complex and disorganized structure which generally characterizes an infected host cell can present a formidable task. Consider, for example, that a high resolution micrograph may show 1/20 of the lateral dimensions and 1/1000 of the thickness of a single cell within a lesion containing thousands of affected cells. The possibility of errors in interpretation due to deficient sampling of changes accompanying pathologic states becomes a factor to be reckoned with and should be constantly borne in mind when reading the increasing number of papers reporting data obtained by these techniques. At present no definitive account can be presented of the structure or development of any animal virus. The illustrations below are offered as characteristic examples of the type of information electron microscopy provides. They are not intended to represent completed or definitive studies.

Herpes Simplex Virus[11,12]

Figure 1 shows part of the nucleus of an epithelial cell. Dense, marginated, reticular material lies against the nuclear membrane which traverses the lower left portion of the field. Adjacent to, and partially replacing, the reticulum is an aggregate of small dense particles, averaging 40 mμ in diameter. Among them is one particle with an incomplete peripheral membrane. Above and to the right, slightly larger particles with a distinct single membrane are scattered through the nuclear

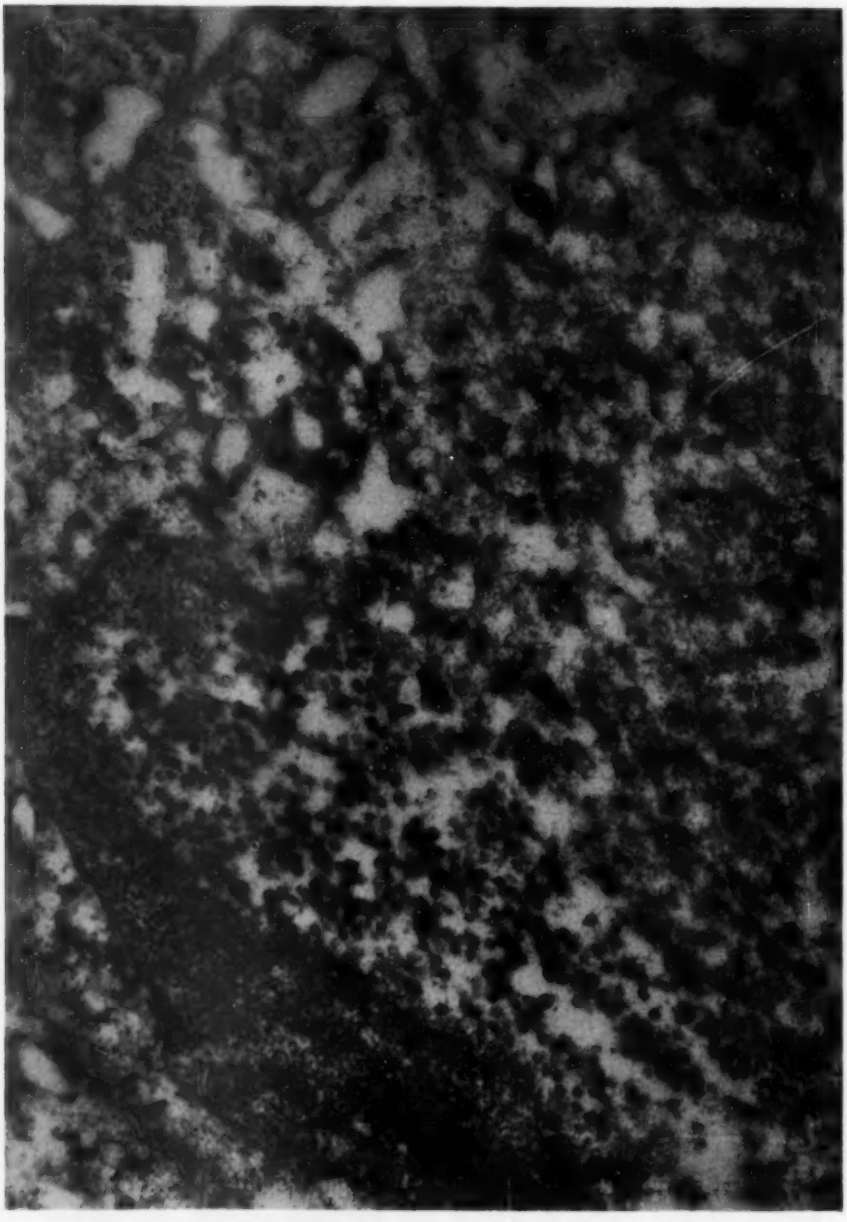

Fig. 1—Magnification = 54,000 x.

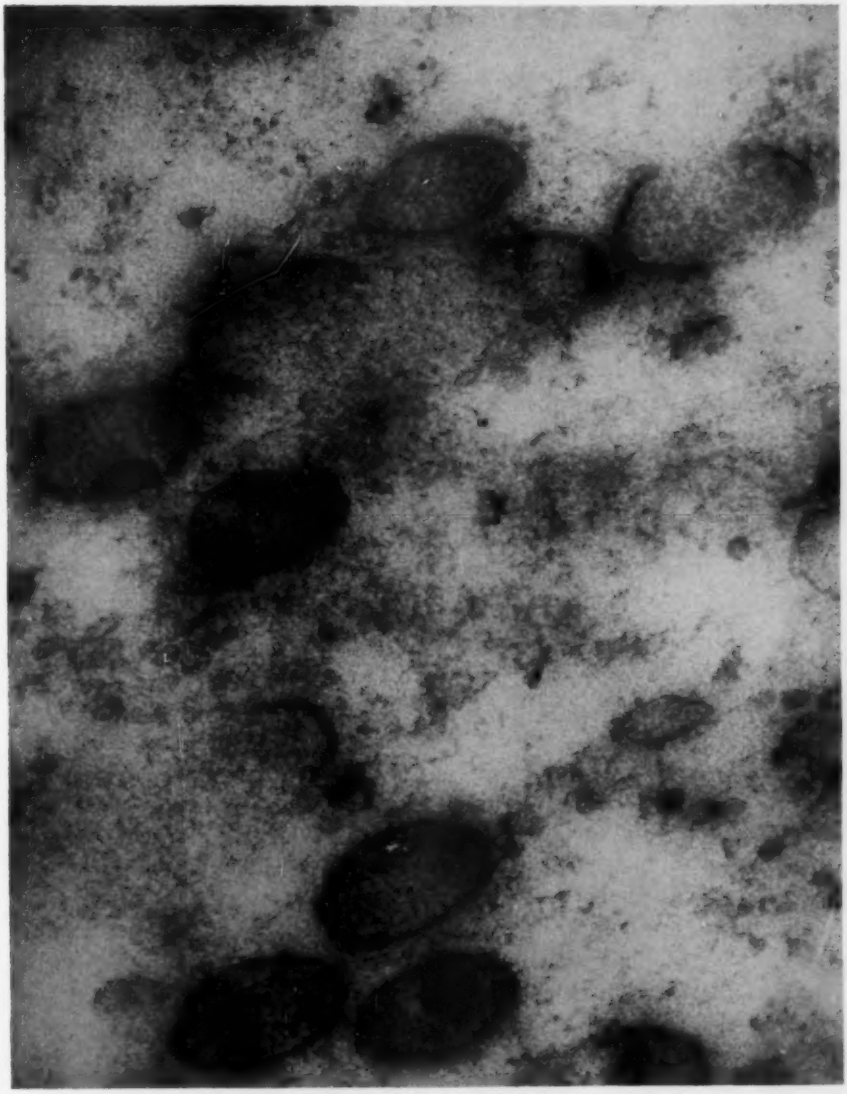

Fig. 2—Magnification = 85,000 x.

matrix. Half way up the left margin the nuclear membrane turns and passes toward the upper right corner. It appears discontinuous in this area, due either to actual interruption or to the fact that parts are oblique to the plane of section. In the upper third a particle with a double limiting membrane lies in the cytoplasm.

Although we have found it impossible to infect a sufficient number of cells with a single inoculum to assemble significant, chronological, electron microscopic data on viral development, study of many cells at the center and periphery of focal lesions in chorioallantoic membranes has permitted a logical sequence to be presented. One is led by pictures, such as that presented above, to the conclusion that a small primary body (c. 40 mμ in diameter) differentiates within the nucleus from dense reticular material, which is utilized by the developing virus. The primary body is enclosed by a limiting membrane and upon release from the nucleus apparently acquires a second membrane in the cytoplasm, this form (averaging 120-130 mμ in diameter) probably constituting the infectious unit found in the extracellular space.

Fowl Pox and Vaccinia Virus[13-16]

In contrast to herpes simplex these viruses are relatively large (c. 250 mμ in diameter) and appear to develop entirely within the cytoplasm of the host cell. Figure 2 shows a group of fowl pox particles.* They possess a limiting membrane enclosing granular matrix. Serial sections[17] indicate that the majority of viral particles at this stage of development contain a dense, eccentrically placed internal body. Since seven to eight consecutive sections are required to visualize an entire particle, only a small proportion of the virus in any given section will exhibit the dense body. Near the top of the picture, finely granular material resembling viral matrix is partially enclosed by incomplete membranes.** Study of many fields showing similar morphology suggests that these membranes are in process of formation and that such sites represent foci of viral differentiation.

As the viral particles approach the cell surface they apparently become altered. Figure 3 illustrates vaccinia virus*** at a late stage of

* As in the case of herpes simplex, these particles were undoubtedly spherical, their present ellipsoidal shape representing distortion produced by the microtome knife, which passed vertically across the field.

** It will be remembered that incomplete membranes were also encountered in micrographs of herpes simplex (see Fig. 1).

***Fowl pox and vaccinia virus exhibit similar, though not identical structure, at comparable stages of development.

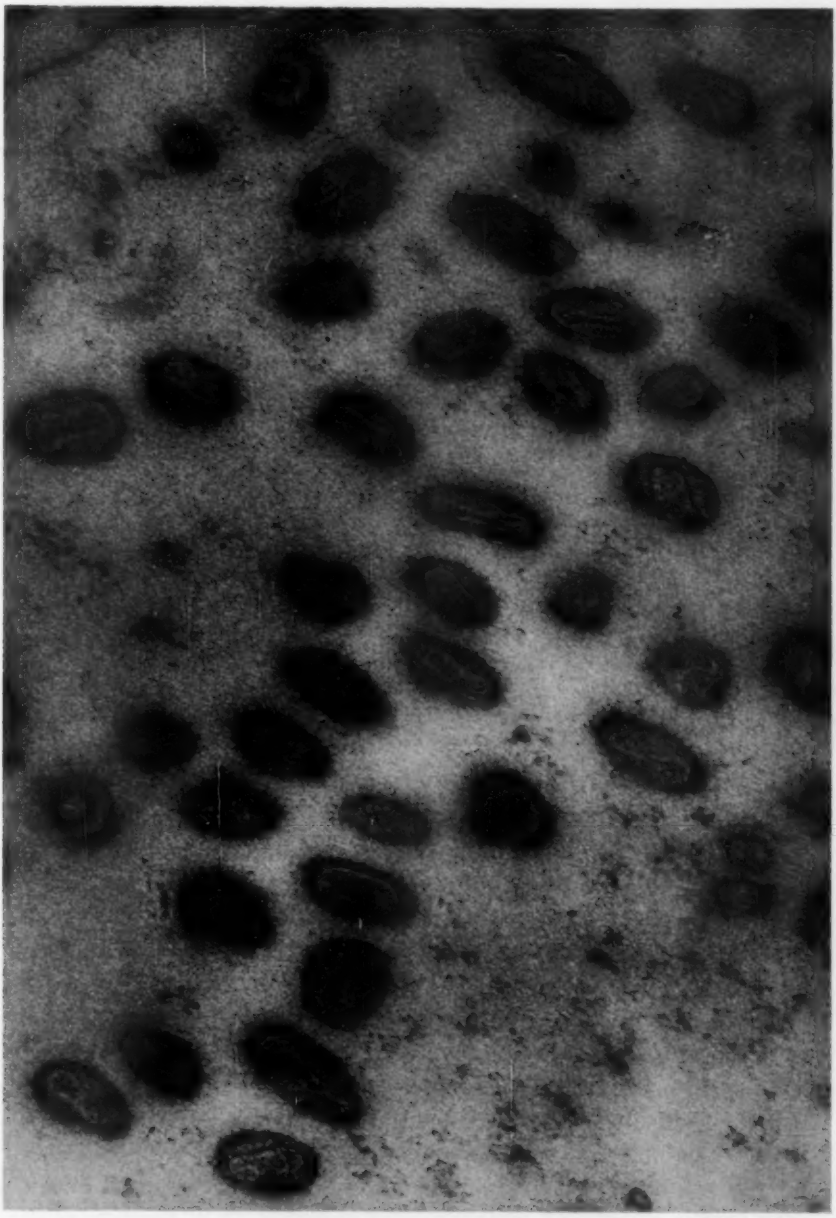

Fig. 3—Magnification = 71,000 x.

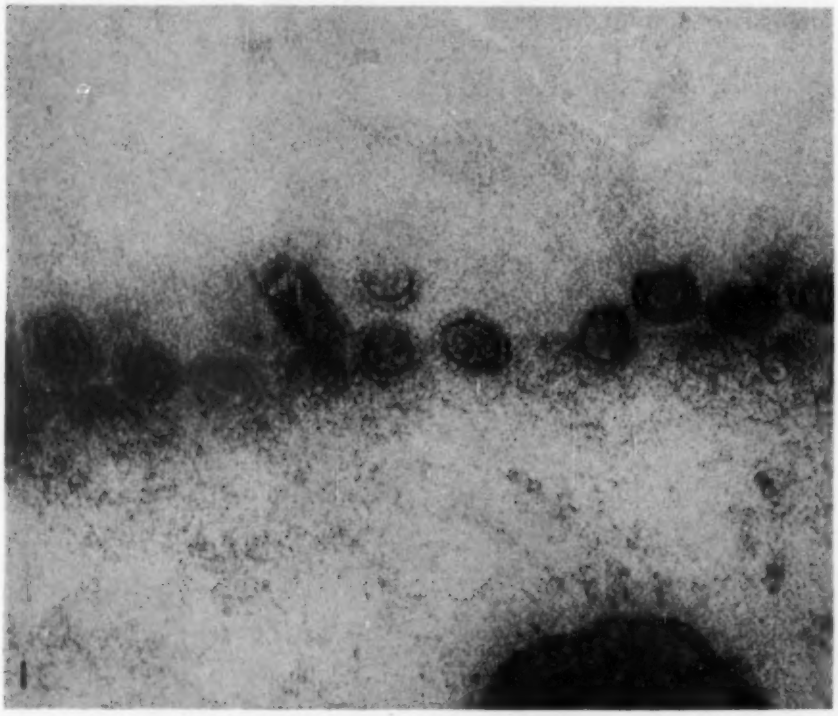

Fig. 4—Magnification = 150,000 x.

development. The various shapes can best be explained by assuming that the virus is an oblate spheroid. The internal body enclosed by dense matrix resembles a biconcave disc cut at different levels and varying in orientation with respect to the plane of section. Several particles exhibit double peripheral membranes, which are characteristic of fowl pox and vaccinia virus in the final stage of development.

Recently, Peters[18] has published micrographs of sections through pellets obtained by centrifugation of infective chorioallantoic fluid. The structure he observed after osmium fixation was similar to that shown in Figure 3, suggesting that such forms represent the completed infectious units.

Influenza Virus[19]

The electron microscopy of influenza virus has posed a difficult problem for three reasons: 1) It is relatively small for detailed examination of internal components; 2) two distinct forms, filaments and spheres, have been observed;[20] 3) artifacts produced in specimen preparation have led to the widely accepted,[21] but apparently erroneous conclusion,[19] that the spheres develop primarily by segmentation of the filaments. Present techniques permit study of this virus in more detail and with less distortion than was previously possible. Figure 4 illustrates the surface of an epithelial cell on the entoderm of a chick chorioallantoic membrane. The allantoic cavity occupies the upper half of the field; the cytoplasm of the cell, the lower half. Spherical forms of influenza virus are apparent at the cell surface. In the right third, one particle, which was probably central to the plane of section, exhibits a dense central body, a sharply defined membrane and a diffuse outer coat. In the left third of the micrograph is a short filament. The absence of a clearly defined membrane at the distal end suggests that this filament was sectioned obliquely. The filaments possess no clearly defined internal structure, although the peripheral coat and dense membrane closely resemble components of the sphere. Such observations are consistent with the fact that both forms agglutinate red blood cells. Whether both are infectious, however, remains to be determined.

Study of many micrographs frequently revealed filaments and spheres at different sites on the host cell. Moreover, segmentation of the filaments was rarely encountered. Such observations suggest that these two viral forms develop in an independent manner. The filaments probably form by a process of budding. Initially they contain moderately dense, amorphous material but as they increase in length their interior becomes devoid of recognizable structure. Having achieved a variable length, the limiting membrane appears to enclose the end proximal to the cell and the filament is released. The spheres, on the other hand, seem to differentiate at or just beneath the cell surface, probably acquiring their structure as they pass out through the cell wall. Of interest is the observation that large numbers of viral particles can be produced by epithelial cells of chicken chorioallantoic membranes in the absence of recognizable cytopathogenic effects.

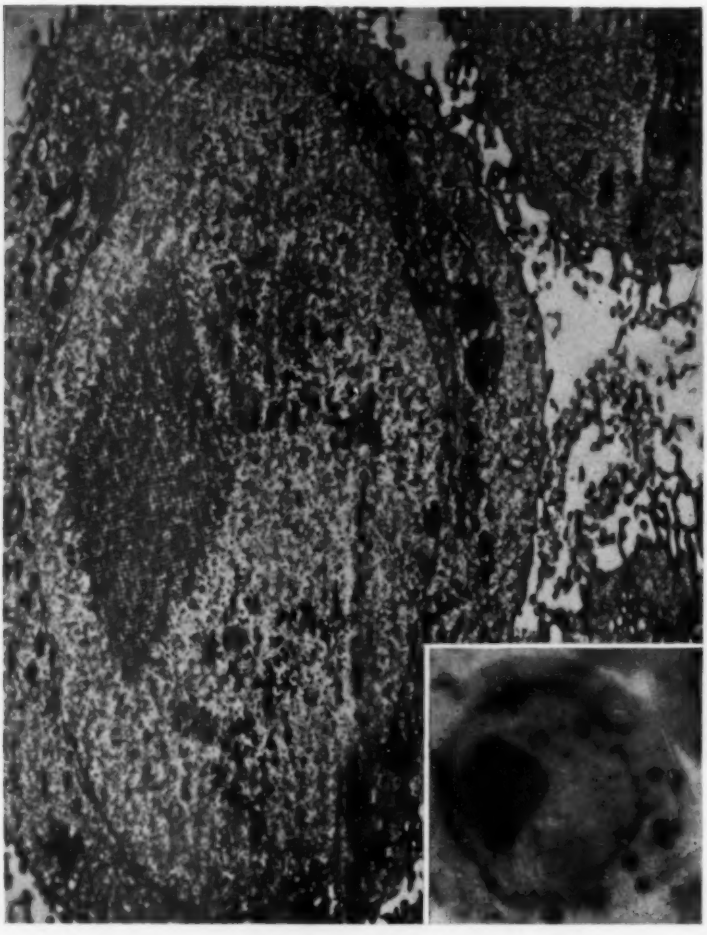

Fig. 5—Magnification = 7,500 x.

Adenoviruses[22-24]

This group lends itself to study with both the light and electron microscope, because large crystals composed of viral particles are repeatedly encountered. The virus appears to differentiate from dense, intranuclear aggregates of reticular material, the spherical viral particles

averaging 60 mμ in diameter. While still within the nucleus the virus frequently forms crystals,* which achieve variable size and then disintegrate. Micrographs at high magnification of very thin sections reveal two distinct morphologic types of particles: one very dense, the other of low density, exhibiting a small central body. At any stage the nucleus may rupture, releasing virus into the cytoplasm.

Obviously individual viral particles cannot be seen in the light microscope, but some crystals are large enough to be plainly visible. By cutting contiguous thin sections for the electron microscope and thick sections for the light microscope, it has been possible to examine the same cell with both techniques.[26] Figure 5, for example, shows a nucleus containing a rhomboidal crystal. The inset at the lower right illustrates the same crystal stained by the Feulgen technique and photographed in the light microscope. Since the crystal composed of viral particles is Feulgen positive, it is likely that the virus contains DNA. In this way the resolution of the electron microscope can be used to define components stained for the light microscope.

Recently, examination of type 5 adenovirus has revealed intranuclear crystals which, while occurring only within infected cells, are not composed of viral particles.[27] Figure 6 shows a nucleus containing virus distributed at random and a large crystal with six flat faces. (The striations are probably produced by overlapping molecules.) Comparison of contiguous thick and thin sections reveals that such a crystal is Feulgen negative, whereas viral aggregates are positive. Whether such crystals, devoid of recognizable DNA, are analogous to the abnormal proteins associated with several plant viruses[28] or to the polyhedral crystals [29-31] observed with certain insect viruses, remains to be determined. It is possible, however, that chemical and immunological analysis, combined with further morphologic study, of these two types of crystals may throw considerable light on the obscure mechanisms of viral development.

If the preliminary observations presented above provide little information concerning the true nature of viruses, they do show that a beginning has been made in visualizing their structure. These observations at least permit us to raise questions unthought of a few years ago.

* It has been possible to deduce the likely lattice structure from examination of viral arrangement in thin sections.[32]

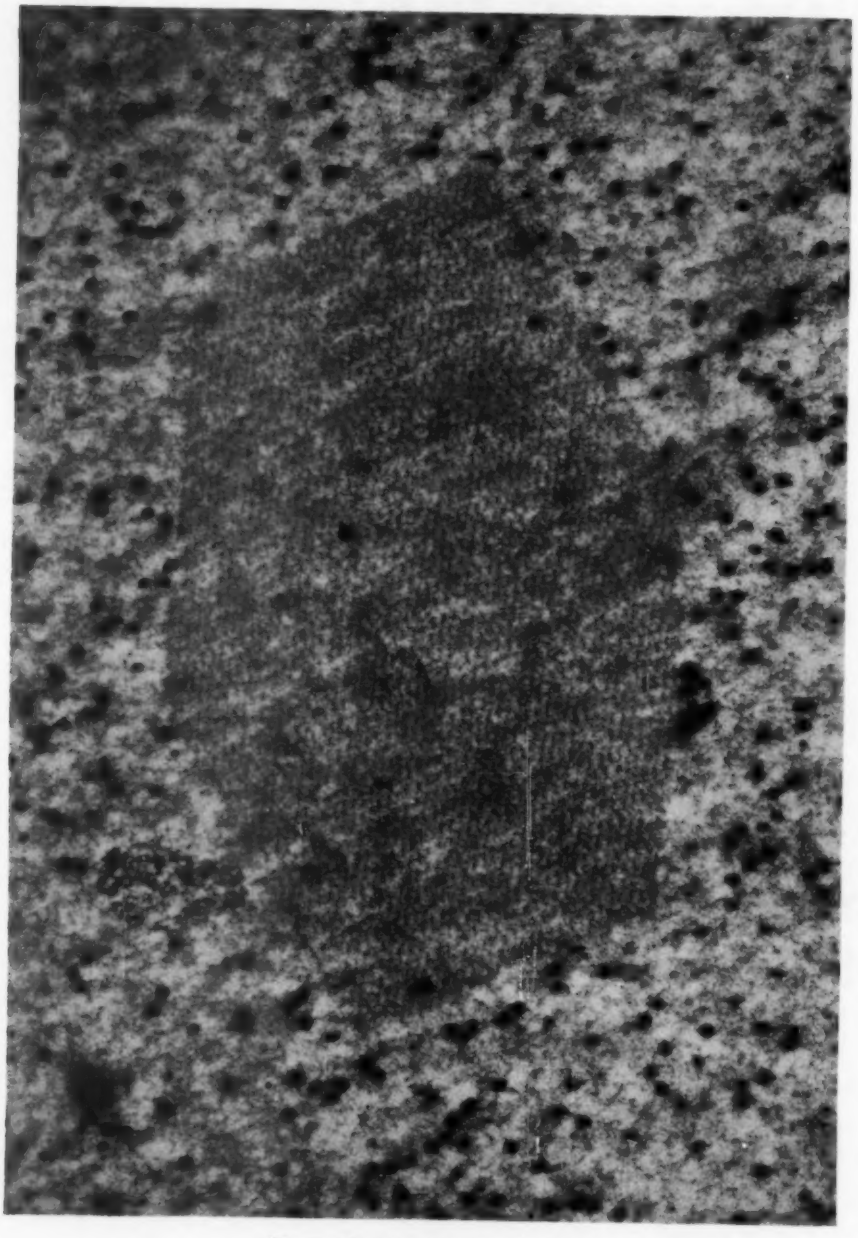

Fig. 6—Magnification = 33,000 x.

For example, is the second membrane enclosing herpes simplex virus merely protective or does it contain important antigenic components? Does the dense body in vaccinia and fowl pox represent the nucleic acid responsible for self-replication? What components of the host cell are present at the surface to instigate differentiation of influenza virus there? What is the significance of the structural differences observed in the two types of adenoviral particles? Why is it that crystals lacking viral structure are associated with type 5 adenovirus, whereas such crystals have not been encountered in types 1, 2, 3, 4, 7, or 8?

The answers to these questions and to a host of others will depend on further definition of the relationship between structure and function. Thus far little correlation has been evident between the morphologic characteristics of animal viruses, on the one hand, and their chemical composition, as well as their effects upon the host cell, on the other. Obviously studies to delineate the features of this correlation must be vigorously continued.

The authors gratefully acknowledge the technical assistance of Miss Dorothy Gelber and Mrs. Florence Lamberts.

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STUDY OF ALCOHOLISM WITH ONSET FORTY-FIVE YEARS OR OLDER*

HARRY H. MOORHEAD

OVER the years a number of studies have been made at the New York Hospital-Westchester Division on patients who have been admitted with the problem of alcoholism The average age of these patients at the time of admission was in the fourth decade. Wall, in his study of alcoholism in women, found that those who began their excessive drinking in the third and fourth decades of life showed a period of moderate social type of drinking preceding the onset. In this particular group he noted such etiological factors as incompatibility in marriage, guilt and conflict over an extra-marital affair, jealousy, childbirth, physical disease, and deaths of relatives. He noted that five patients who began to drink after age 40, were passing through the menopause. These findings suggest the need to attempt to distinguish between the person who in the first three decades is able to lead a successful life with considerable alcoholic consumption and the one whose drinking becomes a problem in later life.

Between 1939 and 1953, a 15-year period, 61 hospitalized patients were studied, both male and female, in whom drinking posed a problem serious enough to compromise their adjustment to life at 45 years of age, or older. This study concerns itself with these 61 patients. There were 41 men and 20 women. Their average age at the time of admission was 55. The diagnoses were as follows:

	Male	*Female*	*Male & Female*
Without Mental Disorder: Alcoholism	33	11	44
With Alcoholic Psychosis:			
Delirium Tremens	5	3	8
Acute Hallucinosis	0	2	2
Acute Paranoid Type	1	0	1
Alcoholic Deterioration	1	3	4
Korsakoff's	1	1	2
TOTALS	41	20	61

* Presented at the *Residents' Meeting* at a combined meeting of the Section on Neurology and Psychiatry with the New York Neurological Society, at The New York Academy of Medicine, May 14, 1957.

It is of interest to note that almost 50 per cent of the 20 women had alcoholic psychosis which is double that of the male group.

Forty-seven of these patients came to the hospital of their own volition and either petitioned for certification by the court as inebriates for a period of care and treatment of from six months to a year, or were admitted on their voluntary application. In the remaining 14 patients the presence of mental illness of psychotic proportions required that they be admitted on court certification or on a physician's certificate. Four patients elected to follow the advice of the staff and stay on as voluntary patients after either their inebriate certification or court certification had expired. The average duration of hospitalization in the whole group was a little less than six months. It is of interest that those patients who were admitted on a voluntary application stayed only an average of three months, and none of these patients has been found in the abstinent group on the follow-up. Fifty-six patients had only one admission, and five required two admissions because of return of their problem shortly after leaving the hospital. The average duration of hospitalization of the 11 patients who became abstinent was nine months.

A review of the family background in these cases was of significance. Forty-four cases were positive for alcoholism, mental disorder, suicides or attempted suicides, in the patient's generation or the two previous generations. There were two suicides and two attempts at suicide. It is of interest to note that there were ten instances of spontaneous abstinence without treatment. Two of the 11 patients in this study, who became abstinent, had this occur in their ancestry. Five of these 11 had negative family histories.

There were a number of significant factors in the early life of these patients. There were 15 instances of broken homes, usually due to the death of a parent, divorce, or separation. In eight instances the patient was an only child. Over-attachment to the parent occurred in 24 instances, the majority being in the patient-mother relationship. There were three or more siblings in 43 cases. Of the 11 patients who went on to become abstinent, only one was an only child, and the others had anywhere from two to 11 siblings. Also, five of the abstinent group came from what were described as abstinent, temperate, or puritanical homes.

From the intellectual standpoint, these patients represented an above-

average group. Sixteen had completed high school and another 15 had completed part of college. There were seven college graduates and ten had finished professional schools. Only five claimed no occupation—this was exclusive of the female group, the great majority of whom were housewives. Fourteen were, or had been, associated with various professions, and 23 were in business activities. There was one farmer. One of the group of men had retired.

Reported religious affiliations indicated that 41 were Protestant, 16 Roman Catholics, three Hebrew and one unknown. At the time of admission four had remained single, 34 had been married once, eight had been married but were now separated or divorced, ten had married two or more times, and seven were widowed. The average age of the first marriage in the male group was 31 years, in the female, 26 years. There were 17 childless marriages and 28 with two or more children. Only 11 marriages were reported as happy, with a satisfactory sexual adjustment in six. Low sex interest, shyness, extra-marital affairs, impotence, frigidity, demanding spouse, were reported 28 times.

Constitutionally there were 27 of pyknic habitus, 15 of asthenic habitus, 15 of athletic habitus, and two of dysplastic habitus. One was described only as obese. There were a multiplicity of physical abnormalities with tremor, liver enlargement, hypertension, poor oral hygiene, malnutrition, and evidence of arteriosclerosis predominating. In eight there was laboratory evidence of liver dysfunction. There were three abnormal EKG's, two abnormal EEG's, and one positive Kline reaction.

In 20 of the patients, drugs had been used in various amounts along with the alcohol and for the after effects of alcohol. The drugs most frequently listed were barbiturates and bromides.

Four patients had attempted suicide prior to admission to the hospital. One consciously recognized that he was using alcohol for this purpose.

Eight patients began to drink for the first time between the ages of 40 and 50; 38 between 20 and 39; four during adolescence, and one before the age of ten. In the case of the men the average age of onset was 27 years, and among the women it was 36, giving a mean average of 30 years. The mean average age when drinking became a problem, and interfered with their life adjustment, was between 49 and 50 in both the male and female groups. Thus, there was a 19-year span

between the onset of drinking and the time when it became a problem.

The basic drinking pattern, prior to the onset of alcoholism, fell into a number of fairly well-defined groups. Fifteen cases could be categorized as periodic excessive drinking, 13 as heavy social, 16 as moderate social, and five as light social drinking. Four drank specifically for energy, or because of fatigue, insomnia, or stress. One had been opposed to drinking, one drank "little if any", and two had had long periods of abstinence.

The amount and character of drinking, after alcohol had become a problem, was found to be rather ill-defined. The patients tended to minimize the amount and the relatives were inaccurate because much of the patient's drinking was solitary. Nevertheless, in 45 patients, the amount varied between one pint to over one quart of hard liquor in a 24-hour period. The character of the drinking included sprees, steady, morning, evening only, and solitary. In the majority of the cases susceptibility to alcohol increased once alcohol had become a problem. Eating habits were reported as poor in 24 patients, with no data in 32 of the 61 cases under study.

As in other studies of alcoholism done at this hospital, no typical personality make-up was found. Family over-attachments involving mother, father, siblings, or spouse were reported 38 times. The group in the study that did well exhibited the same wide variety of personality traits, but as a group showed better personality organization, less rigidity, and more energy.

The reasons for drinking, as stated by the patients, could be grouped into endogenous and exogenous factors. As Prout found to be true in his recent study entitled, "Current Issues in Addiction Research", this group of patients presented a number of descriptive terms which could be considered as endogenous factors, and their drinking produced either relief of certain unpleasant feelings, or contributed new and pleasant feelings.

The patients gave a variety of exogenous factors as reasons for their drinking, but these were usually accompanied by endogenous factors. In their order of frequency: job dissatisfaction, including semi-retirement and retirement; death, loss or threat of loss of a member of the family or a loved one, including separation and divorce; dissatisfaction with parents, in-laws, siblings or children; physical disability; menopause; nervous parents; and social or business influences. In analyzing

the records of the patients it was obvious that the informants placed a greater emphasis on the exogenous etiological factors. The order of frequency paralleled what the patient said, but greater emphasis was placed on physical disability, aging, and involutional factors. The increased ability of the abstinent follow-up group to manage the exogenous factors seemed to be important in their making satisfactory progress.

In a study of the mental status examination, at the time of admission, findings in the non-psychotic group in their order of frequency were: a marked tendency to minimize drinking as a problem; a combination of a critical attitude, irritability and defensiveness; hostility toward members of the family; guilt over drinking; and depression of mood. In 12 cases there was a definite sensorium defect, and in 11 instances there was a marked depressive trend. In the psychotic group where there were delusions, hallucinations and marked organicity, there were productions such as a wish to die, fears of aging and loss of spouse, and confusion between brother and husband which ultimately proved helpful in understanding some of the patient's problems.

Psychological studies were done on a little over half of the patients in this study. The mean I.Q. obtained was 116. Organicity of varying degrees was found in 21 patients shortly after admission. Several patients with organicity at the time of admission were subsequently tested and showed lessening of organicity as hospitalization progressed. As far as the personality was concerned, no one type was seen. Common finding was a level of immaturity for their years, often associated with sensitivity, irritability, and self-centered ways. Some of this group were depressed and fearful, more like other patients of their age. Others showed a wilfulness, hostility and stubbornness more characteristic of younger patients, possibly of psychopaths. There were others who seemed to have reacted to fear and loneliness and were struggling with their religious beliefs, concern over their physical health, etcetera, which is similar to the concerns of the involutional period. The most frequent tests used in the psychological studies were the Rorschach, the Wechsler-Bellevue, the Minnesota Multiphasic Personality Test, and the TAT.

Predominant behavior reaction to the controlled situation that the patients found in the hospital fell rather neatly into two types. Thirty-five of the patients were acceptant, cooperative and at ease; 18 were rebellious, critical, restless, and irritable throughout their hospitalization.

The majority of patients who went on to become abstinent fell in the passive group.

In 13 of the patients there occurred a significant change in their life situation, on leaving the hospital, which led to greater security. Such changes were: separation from spouse, living with a companion or compatible relative, reduction in work responsibility, remarriage, broadening of interest, and a move to an area of less social pressure. In eight of the 11 patients who became abstinent, there were such changes.

A follow-up study was done on these 61 cases. The results have been statistically classified as follows:

	Male & Female
Abstinent	11
Managed better	16
Died during hospitalization	3
No change	19
No follow-up	12
	61

The average age of the abstinent group was 56, and the span of follow-up was from 2 years to 12½ years, for an average duration of follow-up of 6.2 years.

Two patients, after having abstained for seven and six years, respectively, died of heart attacks. Of the remaining group 14 patients died: four from heart attacks; three deaths were associated with alcohol; two died of pneumonia; one of a bleeding gastric ulcer; one of suicide; and in three the cause of death was unknown.

As far as care and treatment of the alcoholic patient are concerned, experience has shown that the patient requires a prolonged period of abstinence and re-education. At the New York Hospital-Westchester Division a period of 12 or six months' hospitalization is recommended. It is required that the patient, in a sober condition, petition for his own certification on an "Inebriate Certification" form. Within the first few days he is examined by two physicians not associated with the hospital, and they certify that he is an inebriate and a proper subject for treatment. The patient is then certified to our care by a judge of a court of record. In some instances the patient is accepted on a voluntary application, but this has been found to be unsuccessful as voluntary patients usually leave before much has been accomplished, and the dis-

couraging effect of another failure adds to the burden of the patient and his family. Immediately upon admission all alcohol is withdrawn. The patient receives a thorough physical and neurological examination. Complete laboratory studies are done. Any physical illnesses are treated as they appear. The psychotic alcoholic who is usually depleted physically, is treated vigorously with the usual appropriate measures including vitamins and insulin and glucose. The alcoholic patient is given a nutritious and vitamin-rich diet. Hydrotherapy and massage are found particularly helpful in reducing the patient's restlessness and tensions. Within a few days the patient is on a well-planned program of occupational therapy and recreational and social activities. The patient is assigned to a physician who plans and carries out psychotherapy, as well as supervising his daily activities. Once the physician has the confidence of the patient an effort is made to help him put aside his many defensive mechanisms and face his underlying, rather tragic personality structure. He must be taught to appreciate that he cannot drink again. After a period of time in the hospital the basic personality structure of the patient begins to appear. In some it appears that the patient's compulsive drinking was a reaction to a difficult life situation. In these individuals a shorter period of re-education is all that is necessary. They are encouraged to assume a normal life sooner than those with more involved inner problems. Frequently the individual has the neurotic problem of tension and anxiety, and has been drinking to escape the associated feelings. The person may be shy, sensitive, or schizoid, or the psychopathic type who is boastful, argumentative, and aggressive. Another group seen more frequently with the increased span of life of today, are those developing cerebral arteriosclerosis with the inebriety associated with this clinical picture.

As the patients progress through the hospital they are gradually given increased responsibility and freedom. At first they are likely to be too ambitious and show poor planning in their activities, and inclined to be irritable with supervision. During the last weeks of treatment they are encouraged to visit their homes and resume work. If there are difficulties in their life situation they are encouraged to remain on in the hospital until these have been worked out. Social service contacts with the patient or the families have been of great help in working these problems through. If the patient desires to remain longer than his six months' or year's certification, he may be readmitted as a voluntary

patient upon the expiration of the inebriate commitment. The transition period from the hospital to home or work offers an opportunity for effective psychotherapy. The patient is encouraged, toward the end of his hospitalization, to make contacts with Alcoholics Anonymous, if this is deemed advisable. Many of the patients, even after leaving the hospital, continue to see their physician.

A brief abstract of a case history will aid in illustrating some of the above findings:

Case of Mrs. J. B. G.: Of English-Scotch and Irish Roman Catholic stock, Mrs. G. was admitted to the hospital at age 59 on her own petition for inebriate certification, in which she stated that she had been drinking to excess for a nine-year period following her husband's death, because she was depressed, had no outlook on life, and one sickness after another. She said she got into the habit, which seemed to help at first, and then, after a time, it hurt her more than it helped her. Her father had been a heavy spree drinker and during one of these episodes made a homicidal attack on his wife, following which he was sent to prison for five years. During middle age he became overly religious and remained abstinent until his death in his 80s. A sister had a psychotic depression. The patient was the 5th of 7 siblings and said to have been her father's favorite. She attended parochial schools and graduated, at 22 years of age, as a registered nurse. She practiced nursing in her home town, and at 30 years of age married the son of one of her patients, a man a good many years her senior. At 33 years of age, after a complicated labor, her only child was born by caesarian section. The patient was extroverted, energetic, and made a good adjustment as a trained nurse and later as a wife and mother. She was a respected leader in many community activities. However, she tended to lean heavily on her husband, who took the responsibility for many of the more practical details of their lives. When she was 43 her husband developed heart trouble and she nursed him through several illnesses prior to his death, when she was 49. She did not show any emotion following his death and kept up for her son's sake. She did not fully realize her loss until her son had left for school, leaving her alone. Except for a number of abdominal operations for adhesions and a hysterectomy, attacks of sinusitis, and several asthmatic attacks early in her marriage, her physical health had been excellent.

After her husband's death she was lonely and began to drink to keep her spirits up. She spent many hours in bed in the morning, and over the next several years her drinking increased and extended throughout the day to the point of stupor in the evenings. When intoxicated she would get sentimental and frequently cry. The only people in the home were servants, with an occasional visit from her son who was away at school.

When she was 57 her son entered the army and this was an added blow to her. It was around this time that she fell and fractured several vertebrae while

intoxicated. During her hospitalization she developed delirium tremens. Shortly before admission to the hospital her condition resulted in her son's release from the army, and on his return he found her depressed and irritable, drinking up to a quart of whiskey daily. Her son's threats to leave the home precipitated her hospitalization. Mental status on admission showed her to be emotionally labile with her spontaneous productions and associations connected with her dead husband and her married son. She admitted to difficulty with drinking and reasoned that it resulted from her loneliness after her husband's death. She said that she drank to get a lift and to forget the past. She exhibited anxiety and mild hypochondriasis. Her sensorium was intact. She displayed good insight into the fact that she needed treatment for her drinking, but her judgment seemed swayed by sentimentality. Physical examination, following admission, revealed her to be obese and of pyknic habitus. There were two surgical scars of the abdomen, osteo-arthritis of the hands, and liver enlargement. The laboratory studies and x-rays were negative, except for a mild anemia. She adjusted quickly, comfortably, and cooperatively to the hospital. She soon was able to engage in a full program of activities. During her third month she was moved to an open, convalescent hall and began to visit out for short periods of time with her friends and son. She gained a sense of security from her hospitalization, particularly from the companionship and the routine of the activities. She had an episode of sinusitis and some stiffness of her knees, which were treated symptomatically and improved rapidly. She spent several weeks with her son and found this unsatisfactory to both of them. At the end of her inebriate certification of six months she had not worked out her future and she was readmitted to the hospital on voluntary status. When threatened with separation from her son she began to express some fears of loneliness, but gradually accepted separation, and saw her son's need for emancipation. She accepted the idea of a companion and a suitable arrangement was worked out for her. She was able to leave after 14 months in the hospital. Periodic follow-up reports from the son indicate that she has been totally abstinent since discharge. The most recent report, eight years after discharge, indicates that she is bothered with periodic intestinal upsets and arthritis, but is living with a housekeeper and able to drive her own car.

Discussion

Little can be concluded from the data presented. However, the study suggests that alcoholism is as malignant a disorder in the older age group as in the younger. In studies previously done at this hospital, in which the average age when drinking became a serious problem was approximately 35 years, there was a recovery or abstinent rate of 25 per cent as compared with 18 per cent in this study. The same hereditary and environmental factors were similar in the two groups. Also the

wide variety of personality traits, without one typical personality make-up, was a similar finding in the two groups. The personality inadequacies and the external stress seem to be essentially similar except that in the older age group the stress manifested itself differently, as would be expected in middle or older age. Just how much, is uncertain, but aging and its consequences undoubtedly influenced the outcome of treatment in this group of older alcoholics.

As brought out in the data presented there were differences in the abstinent group when compared with the group as a whole, however these differences were not to the point where they could be considered significant. The author felt that the abstinent group showed better personality organization, less rigidity, more energy, and as a result were better able to manage the stress factors in the environment which contributed to their problem.

Summary

1. A study has been made of 61 patients in whom alcohol became a problem at 45 years of age, or older.
2. A statistical review of hereditary and environmental factors is presented.
3. Hospital management has been briefly discussed.
4. Results of follow-up studies are reported, indicating that 11, or 18 per cent, became abstinent, and 16, or 26 per cent managed better, for a total of 44 per cent definitely benefited.

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THERAPY OF INFECTIONS

*Transcription of a Panel Meeting**

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* Presented at the 29th Graduate Fortnight of The New York Academy of Medicine, October 26, 1956.

MODERATOR DAVID E. ROGERS: Ladies and Gentlemen, the subject before us is an extremely broad one. We have therefore agreed to confine our remarks to certain infections which have gained in importance in recent years and to areas of therapy undergoing rapid change.

The treatment of staphylococcal infections has been receiving increasing attention. Dr. Woodward, are you admitting more patients with staphylococcal infections to your hospital in Baltimore?

DR. THEODORE E. WOODWARD: It is my conviction that we are encountering more patients with staphylococcal disease in the hospital than heretofore. Staphylococcal disease is becoming a hospital problem, more resistant strains are being encountered increasingly often and as patients leave the hospitals they must be exposing the general population to penicillin-resistant strains. Lacking any specific data on this point my answer, purely a conviction, is yes.

MODERATOR ROGERS: Let me make my question more specific. Were more patients admitted with acute staphylococcal infections in 1956 than there were, for example in 1936? In other words, are more patients developing staphylococcal infections *outside* the hospital than in the pre-antimicrobial era?

DR. WOODWARD: It is my opinion that the problem outside the hospital is greater. Patients are being encountered with staphylococcal problems such as furuncles, carbuncles, cellulitis, sepsis, endocarditis and pneumonia. Furunculosis with cellulitis and endocarditis seem to me to be greater in incidence, so it is my belief that more patients with staphylococcal infections are being admitted directly from the outside.

MODERATOR ROGERS: Dr. Tompsett, are you admitting more staphylococcal infections to Bellevue than you did before we had antimicrobials?

DR. RALPH TOMPSETT: I don't know whether I can answer specifically with regard to Bellevue, not having been there all of these past 20 years, but this is one question I should like to be able to answer definitely. There is no question that more of our waking hours are spent in the management of staphylococcal infections than ever before and the time involved is increasing every year. My impression would be that we are seeing more patients with serious staphylococcal infections admitted to the hospital than previously, but probably some sort of an average is struck in that there may be more infections occurring but

with some of them being handled outside the hospital. Therefore, although we see about the same number, they are more serious. I just don't think we know the answer to that question.

MODERATOR ROGERS: Do you have any comments on this problem, Dr. Chaves? Dr. Kilbourne?

DR. EDWIN D. KILBOURNE: I would like to give three answers. The first is, I don't know. The second answer is that I have the impression that staphylococcal infections are not increasing as problems on admission, on total number of patients admitted, and the third answer is to refer specifically to a four year experience at Tulane. During that brief time we had some opportunity to get figures on this and we were not impressed by an increased incidence. I can add to this the comparative experience of all the clinicians who had been in that environment for a long time, and they, too, felt there was no particular increase of the problem on admission. I would, however, certainly agree with Dr. Tompsett, that a great deal more of our time seems to be occupied with the management of these patients.

MODERATOR ROGERS: I am interested in the apparent discrepancies between Baltimore and New York. We have recently analyzed the incidence of admission to New York Hospital for staphylococcal infections, comparing the pre- and post-antimicrobial eras. We have found no increase in the incidence of staphylococcal disease as a cause of admission to New York Hospital, but have found that staphylococcal infections arising *within* the hospital are an increasing problem and have caused us serious difficulty.

DR. WOODWARD: Let me qualify my statement to the extent that I think our problem is greater, although we have not made a careful analysis since 1936. My impression is probably not an accurate appraisal of the situation.

MODERATOR ROGERS: *Dr. Tompsett, what is the clinical significance of antimicrobial resistant staphylococci? Is* in vitro *resistance of importance in the treatment of these infections?*

DR. TOMPSETT: I think it is of very great importance, particularly with regard to the penicillin resistance. If one has, let us say, two patients with the same type of staphylococcal infection and one is susceptible to penicillin and the other one is not, but is susceptible to other drugs, penicillin can be used. We much prefer to use it and when usable, it seems to be a very good drug in the treatment of

staphylococcal infections. With the other drugs, even though the susceptibility tests may indicate that the organisms are susceptible, the results are not nearly as good, so that penicillin resistance is certainly of major importance. I am sure resistance to other drugs is also of major, but perhaps not of such great importance.

MODERATOR ROGERS: *Dr. Woodward, do you believe that penicillin resistant staphylococci are more virulent than sensitive strains? In other words, are we creating a group of extremely vicious antimicrobial-resistant staphylococci that are capable of producing more severe infections than we used to see before we had antimicrobials?*

DR. WOODWARD: My impression is that we have created a group of organisms which are causing diseases that are more difficult to manage.

MODERATOR ROGERS: *Do they cause worse disease?*

DR. WOODWARD: I think the disease is the same; whether it is endocarditis or any other localized infection. It seems to be the same staphylococcal disease. We see more of it, and as Dr. Tompsett has indicated it requires more of our time.

MODERATOR ROGERS: *Dr. Kilbourne, do you think resistant staphylococcal infections are more destructive than infections due to sensitive strains?*

DR. KILBOURNE: My experience has, of course, been largely in the antibiotic era, but I think comparative mortality rates indicate that severe staphylococcal infections are still severe staphylococcal infections. One of the most difficult things to prove is the actual virulence of an organism, even when dealing with experimental infections and experimentally controllable situations. I think it is an almost unanswerable question.

MODERATOR ROGERS:. *Dr. Tompsett, how do you manage patients with serious staphylococcal bacteremia?*

DR. TOMPSETT: I would like to date this [October, 1956, Ed.] because I might give a different answer next week. As of today, I think the first thing we try to do whenever possible is to attack this problem surgically if there is anything that can be done surgically. When we are dealing with one that is manageable surgically we have considerably better results, entirely aside from the question of sensitivity to antimicrobial agents. If a staphylococcal infection is severe, at the present time we assume that this is going to be penicillin resistant and we start the patient on another drug. I believe

at this time erythromycin would be drug No. 1. We generally use two drugs in treating patients with severe infections largely because of the difficulty in management. We know that no one drug is sufficiently good so that, by and large, we use erythromycin and chloramphenicol to initiate therapy. Then we get our cultures, do our sensitivity tests and, if found to be susceptible to penicillin, we always use penicillin.

MODERATOR ROGERS: I am interested to learn that you do not initiate therapy with penicillin.

DR. TOMPSETT: Unless the patient has osteomyelitis. In such instances we have found so far that most of these infections are due to penicillin-susceptible organisms, for some reason which I am unable to figure out. But with osteomyelitis we start the patient on penicillin.

MODERATOR ROGERS: *How much penicillin do you use?*

DR. TOMPSETT: We use about 5 million units per day.

MODERATOR ROGERS: *Dr. Woodward, how do you handle patients with acute staphylococcal sepsis where the sensitivity of the organism is unknown when you first see them?*

DR. WOODWARD: I think our rule of thumb is similar to Dr. Tompsett's and for local infections we emphasize the time honored measures. When the local infection has not responded and shown evidence of progression we are inclined to employ a Group 2 antibiotic, such as erythromycin or chloramphenicol. Given a patient with clinical signs of bacteremia with or without signs of endocarditis, we naturally hope that the organism is penicillin-sensitive. Under these conditions penicillin is our first choice. If the organism on *in vitro* testing by the tube dilution method is not too sensitive, we give penicillin but we are inclined to supplement the penicillin regimen with streptomycin. That is the general rule that we have been using in patients who have staphylococcal disease with possible bacteremia, when the heart valves are conceivably involved. We tend to hit quite hard with penicillin.

MODERATOR ROGERS: I believe the setting in which the infection arises has, in part, governed our initial therapy. When patients with acute staphylococcal infections are admitted from the outlying community where they have had no contact with doctors or antimicrobials —this incidentally applies to a fair number of children with osteomyelitis—we have found that their infections are generally due to penicillin susceptible staphylococci. We thus start therapy in this group with large amounts of penicillin. When we have had staphylococcal infec-

tions develop within the hospitals, the reverse has been true. These infections are usually due to penicillin resistant staphylococci and we have thus been inclined to use other drugs in initiating therapy.

DR. KILBOURNE: May I dissent from what seems to be a majority opinion and dissent with the idea of addressing a question to the panel for my own information. It has been my practice always to include penicillin in the management of any patient who has staphylococcal disease and who exhibits systemic signs of toxicity, on the assumption that he should be treated as a case of endocarditis until proved otherwise and therefore be given what is optimal therapy. My reason for always using penicillin is that regardless of where the patient comes from, outside the hospital or inside the hospital, I think all of us have had sufficient experience with patients who apparently show wide discrepancy between the *in vitro* sensitivity of the organism and the results obtained by drug therapy in the patient. There are patients whose clinical pattern of response to penicillin varies in a manner which does not correspond at all to the *in vitro* sensitivity. Regardless of the fact that a highly "resistant" staphylococcus is present they get well with penicillin and not without it. These cases are somewhat difficult to document. I imagine when we get down to statistics, we each may have seen three of four cases of this sort. But I would like to provoke a little discussion on this point and ask why, if this is true or accepted, we don't always give penicillin?

MODERATOR ROGERS: *Dr. Tompsett, I believe you indicated that you don't always start out with penicillin?*

DR. TOMPSETT: Until a year ago we did exactly what Dr. Kilbourne has just described. We acted on the basis of experience in patients with severe staphylococcal infections who were treated with penicillin and streptomycin and who had favorable clinical results, even though the *in vitro* sensitivity tests indicated that they would not respond. We have been treating these patients with penicillin and streptomycin right from the very beginning. I would like to add that this procedure is still followed where there is any suggestion of endocarditis, as Dr. Woodward has mentioned. This of course, does not make much sense from our knowledge of the *in vitro* tests but as Dr. Kilbourne has indicated, the experience is very limited. Nobody sees very many of these patients and even though we believe there may be considerable virtue in this combination, we are at present giving a trial to the other one,

which does make sense from the standpoint of *in vitro* sensitivity tests. I believe that the difference of opinion expressed here only reflects the fact that none of these regimens is really ideal. So it is a matter of trial and error in a situation where no one therapy can be relied upon.

MODERATOR ROGERS: *Do you believe there could be positive harm in using penicillin except in the sense that one is using a drug that may be ineffective?*

DR. TOMPSETT: I think there is at least the possibility of doing positive harm, not from the standpoint of the microorganism but from the standpoint of reactions in the patient. I have had the misfortune of administering two or three drugs and frequently ending up with a patient who exhibits a hypersensitivity reaction to one of them and not knowing which one is responsible. This is an unfortunate clinical situation if more than one drug is given and especially so if you are giving three. This is the only disadvantage that I can see and it is not too serious a one.

MODERATOR ROGERS: *This brings up a question that I would like to explore further. All of you have mentioned the use of combined therapy in treating staphylococcal infections. What evidence do we have that combined therapy is appropriate? Dr. Woodward, can you defend the use of more than one agent in this situation?*

DR. WOODWARD: As a general rule we do not like combination therapy. We prefer one antibiotic in a regimen for some of the reasons that Dr. Tompsett mentioned. Some patients do not do well on one drug alone and one soon discovers that the one drug, even if given in very significant doses, is not doing the job. I can recall a patient with staphylococcal endocarditis who required 18 million units of penicillin a day to keep her blood stream free of the organism and to keep her free of clinical signs of illness. It was difficult to administer this much penicillin over a period of time. However, with appropriate antibiotic sensitivity testing (tube dilution method), it was shown that Terramycin acted synergistically for this particular strain. Terramycin in that particular patient combined with 10 million units of penicillin daily effected a cure.

In another patient I insisted upon giving massive penicillin treatment for staphylococcal endocarditis. The patient had been receiving a combination of streptomycin and chloramphenicol and seemed to be making a slow response. Fortunately the initial strain had been saved,

and when tested in the laboratory it was shown that this was potentially a winning combination. I was wrong in my stand, for this patient did not require penicillin in spite of the creed that we usually adhere to: that penicillin is absolutely required for endocarditis. This patient recovered on streptomycin and chloramphenicol therapy. I do not think there is any basic dissent from the panel's view of treatment of staphylococcal sepsis, with or without endocarditis. I do think that we concur in believing that the problem must be evaluated in the individual patients who, by their reactions, present incontrovertible evidence of results. The patient himself is a pretty good sensitivity test as to what is happening.

MODERATOR ROGERS: *I notice that none of you have voiced concern regarding the development of antimicrobial resistance of staphylococci in a lesion under treatment. I would like to poll the panel on this point: have any of you ever witnessed a staphylococcus which increased in resistance to the drug or drugs which were being given during the treatment of a serious staphylococcal infection?*

DR. TOMPSETT: I have seen this occur with two drugs, streptomycin and erythromycin.

MODERATOR ROGERS: *How about you, Dr. Woodward?*

DR. WOODWARD: At the moment I can recall one instance with erythromycin.

DR. KILBOURNE: With erythromycin but not penicillin.

MODERATOR ROGERS: *Dr. Chaves, do you have any comment on that?*

DR. AARON D. CHAVES: No.

MODERATOR ROGERS: This seems to me an important point. I think we sometimes talk loosely about the dangers of increasing resistance of microorganisms *under therapy*. It has been our experience that staphylococci present in closed infections like endocarditis do not change in penicillin susceptibility during treatment even when therapy is inadequate and relapse occurs.

Dr. Woodward, how do you treat staphylococcal pneumonia in Baltimore and how long do you continue therapy?

DR. WOODWARD: The last patient with staphylococcal pneumonia whom we treated had measles and was given penicillin as a prophylactic measure. Infection of the lung developed during penicillin therapy. The patient made a very adequate response to chloramphenicol. We are using chloramphenicol rather freely in the treatment of staphylococ-

cal disease, as well as erythromycin.

MODERATOR ROGERS: *Dr. Tompsett are you seeing more staphylococcal pneumonia than before we had antibiotics? This has recently been reported in the British literature.*

DR. TOMPSETT: I believe this is such an uncommon disease that one's experience influences his judgment greatly. It does appear though, that there are now more cases of staphylococcal pneumonia on the pediatric wards than were seen in the past. While this is a relatively frequent problem in that department it is so rare in adults that the figures on incidence that any one person could collect would, I think, be almost meaningless.

MODERATOR ROGERS: *How long do you continue antimicrobial therapy in serious staphylococcal infections, Dr. Tompsett?*

DR. TOMPSETT: We are treating these patients for a long time, a minimum of six weeks if they have a very good response and we usually prefer to continue treatment for about that same length of time after they have obviously started to respond.

MODERATOR ROGERS: *What are your reasons for such extended treatment?*

DR. TOMPSETT: I think the principal reason is that these are patients in whom we never know whether or not endocarditis is present. That is the first thing. We know that the endocarditis must be treated for a long period of time. The second reason is, we have had the experience of treating patients who seemed to respond very well, when treated for two or three weeks and then had them relapse after stopping treatment. This happens even in such diseases as osteomyelitis. We have not given this short term treatment for quite a few years now because of this experience, but certainly relapse and the appearance of metastatic abscesses occur frequently enough to persuade us that all of these patients should have long term therapy.

MODERATOR ROGERS: *Dr. Kilbourne, do you have any difference of opinion?*

DR. KILBOURNE: No, only to emphasize how difficult it is to set any hard and fast rules in these situations because of the limited number of cases which we see and the wide variation in this particular disease, depending upon the number of peripheral foci. Some time ago, I rather arbitrarily decided to continue treatment for at least a month after defervescence or after the disappearance of staphylococci from the

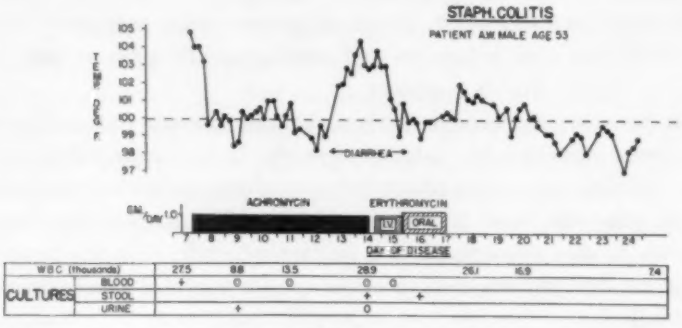

Fig. 1

blood culture. My follow-up of this regimen is inadequate.

MODERATOR ROGERS: *We have recently heard a great deal about staphylococcal enterocolitis as a hospital problem. Dr. Woodward, would you tell us a bit about your experience with this syndrome and how you handle it?*

DR. WOODWARD: I have a slide demonstrating the case record of a patient with this syndrome, if you care to see it.

MODERATOR ROGERS: *Please show it.*

DR. WOODWARD: This patient (Fig. 1) was undergoing treatment for pneumonia during the course of which diarrhea, abdominal pains and shock ensued. An alert house officer made a fecal smear and was able to establish the presence of staphylococcal disease. The patient did quite well on changing the therapy to erythromycin. We have had very few cases. I can recall another patient being treated for pneumococcal meningitis who developed colitis. As we all know this entity occurred long before antibiotics were in clinical use.

MODERATOR ROGERS: *Do you believe that staphylococci were the etiologic agent then?*

DR. WOODWARD: Perhaps there are some in this room who had the opportunity to hear Dr. Ivan Bennett speak before the Association of American Physicians in May of this year. Dr. Bennett presented the case record of a patient who had been operated upon at the Johns Hopkins Hospital in 1893 by Dr. John M. T. Finney. The patient developed colitis postoperatively. In those days this syndrome was called diphtheroid colitis. Dr. Bennett and his associates reexamined the

old preserved tissues and with appropriate staining techniques demonstrated staphylococci on the mucosal surface of the colon.

MODERATOR ROGERS: I think that this is an important point. We have "rediscovered" this disease entity recently. Perhaps it is on the increase but staphylococcal enterocolitis clearly occurred before antimicrobials entered the picture.

Dr. Tompsett, why do patients with enterocolitis die and how should this disease be managed?

DR. TOMPSETT: Too many answers I am afraid. They may die in shock. They may die as a result of the extreme fluid loss before there is sufficient recognition of what is going on. This happens too frequently. They also may die of any of the causes associated with staphylococcus septicemia—endocarditis or metastatic abscesses.

MODERATOR ROGERS: I might summarize briefly before turning to other areas. There is disagreement on the current incidence of staphylococcal infections. Our experience here in New York has led us to believe that staphylococcal infections have not increased as a *cause* of hospital admission but have increased as an intrahospital problem. We appear, in a sense, to have recreated the old puerperal fever wards. Many patients come in for surgery or with debilitating medical illnesses but free of infection and then develop serious staphylococcal infections due to resistant microorganisms. Dr. Woodward believes that perhaps we are admitting more staphylococcal infections than in the past from the outside community.

I think the panelists are agreed that staphylococcal infections probably remain unchanged in virulence. Infections due to resistant strains have gained prominence because of our inability to treat them effectively.

Most of the panelists are agreed that penicillin is the drug of choice when dealing with penicillin-sensitive strains and indeed, in a number of staphylococcal infections, even though they appear resistant in the test tube.

Erythromycin and chloramphenicol have been used in infections thought to be penicillin-resistant from their origin and indeed, Dr. Tompsett is now initiating therapy with these two drugs.

Dr. Woodward pointed out that the patient is a good sensitivity test in himself; if he is clearly responding, the antimicrobials in use should be continued despite laboratory evidence of resistance.

All are agreed that treatment should be continued at high dose levels for a long period of time because of the high relapse rate and development of metastatic abscesses. Dr. Tompsett recommends a minimum of six weeks.

Most of us are not seeing a great deal of staphylococcal enterocolitis. When this disease does occur it is frequently accompanied by shock and great fluid loss. Treatment includes its prompt recognition, withholding broad-spectrum regimens, rapid fluid replacement and the use of erythromycin or novobiocin.

We might turn now to the treatment of rickettsial infections. We have Dr. Woodward with us who has done a great deal of work in this area. Dr. Woodward, how much of a problem are rickettsial infections for us here on the East Coast? Are these infections common or are we talking about a fairly exotic disease?

DR. WOODWARD: As you see, Dr. Rogers is a gentleman because he asked me a statistical question with respect to staphylococcal disease and I feel that I did not do well with it. He is providing an opportunity to discuss more familiar terrain. No, I don't think we have a great incidence of rickettsial disease. We are rapidly going out of business with Rocky Mountain spotted fever in Maryland, the antibiotics are so effective. Physicians treat the patients at home. We are fortunate if we see two or three hospitalized cases a year. There are a few cases of spotted fever to be seen on Long Island. In this city you see some Brill-Zinsser's disease and it is interesting that these patients seem to be concentrated in certain of your excellent New York hospitals. We are dealing largely with a family of infections that are of more importance in other parts of the world than they are in the United States.

May I take a few minutes to summarize certain data pertinent to the rickettsioses?

MODERATOR ROGERS: Please do.

DR. WOODWARD: I should like to show a few slides. The first shows a group of rickettsiae in their intracellular habitat (Slide). These microorganisms find their way throughout the vascular system and choose the endothelial cells as a favorable site. The term "endovasculitis" is adequate to describe the anatomical lesion in patients with typhus fever, Rocky Mountain spotted fever and scrub typhus fever.

Insofar as the management of these diseases with antibiotics is concerned, the physician has been very fortunate because since 1948

TABLE I—RICKETTSIAL DISEASES—1948-1953

Disease	*Drug*	*No.*	*Deaths*
RMSF	Chloramphenicol	43	0
RMSF	Terramycin	9	0
RMSF	Aureomycin	5	0
Murine	Chloramphenicol	12	0
Murine	Terramycin	1	0
Brills	Aureomycin	1	0
Scrub	Chloramphenicol	274	0
	Total	345	0

he has had a group of effective antibiotics with high specificity of action for the rickettsiae. The antibiotics act as rickettsiostatic rather than as rickettsiocidal or killing agents. It will be noted that in the University Hospital in Baltimore, for the 15 year period 1930 to 1945, there were 85 patients with spotted fever who spent about 16 days each in the hospital. The fatality rate was 23 per cent. By contrast, treatment with various of the antibiotics, chloramphenicol and the tetracycline group, has virtually eliminated mortality. Fatality in this disease should not occur. The patient's temperature returns to normal levels two or three days after beginning therapy and the patient feels much better prior to defervescence.

Perhaps there will be time for a word with respect to the use of steroids in combination with specific chemotherapeutic agents.

(Slide) In this slide (Table 1) is summarized the clinical experience for the period 1948 to 1953. In a series of 345 cases of various rickettsial diseases, there were no fatalities. There is little significant difference between the therapeutic effect of chloramphenicol and the tetracyclines. They are all amazingly good.

(Slide) We should emphasize two problems of treatment. The first concerns the administration of the antibiotic to a patient who has had the disease for approximately a week or less. In that instance the antibiotic is enough. Such patients recover with reasonably good supportive care. However, in patients first seen late in the illness when the vascular changes are more pronounced, specific therapy is not enough. These patients require good supportive care as well, and good supportive care means support to the circulatory system. This includes both adequate

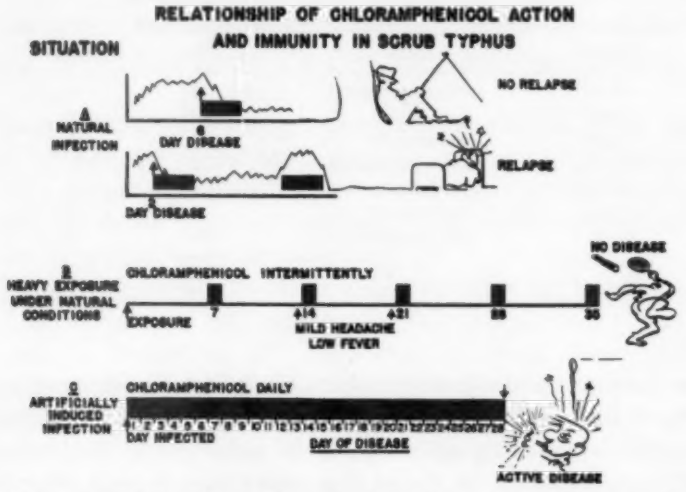

Figure 2.—Relationship of chloramphenicol action and immunity in scrub typhus. Reproduced from Fig. 8 in Woodward, T. E. and Parker, R. T. Clinical application and mode of action of antibiotics in rickettsial and virus diseases, in "International Symposium on Dynamics of Virus and Rickettsial Infections" by Hartman, Horsfall and Kidd. Copyright, 1952. Blakiston Div., McGraw-Hill. (Reproduced by permission.)

protein intake and electrolyte balance. Ordinarily, if one treats the patient with an antibiotic, the temperature returns to normal in a short time. Occasionally there is a relapse about which there will be a word in a minute.

As mentioned previously, corticoids have been used. Cortisone has been administered to patients with Rocky Mountain spotted fever and to patients with typhus fever. Cortisone or its analogues are not needed as a routine expedient but occasionally in an extremely toxic patient one may bring about considerable improvement within 24 hours. One would not hesitate to use steroids in conjunction with antibiotics in the severely ill case but not as a routine measure.

(Slide) I mentioned the problems of relapse. This slide (Fig. 2) gives a summary of the results of approximately three years' experience with the rickettsial disease, scrub typhus, or tsutsugamushi disease as it is known in Japan. Under situation A, note that when the patient is treated for his diseases on about the sixth day, which is the usual time

that the clinical diagnosis is established concurrently with the appearance of a rash, the antibiotic results in prompt defervescence. Moreover a patient treated at this stage does not relapse. In scrub typhus patients, (but rarely in spotted fever, I have only seen it in one or two instances) when the disease is detected quite early, one is able to make an accurate diagnosis. With treatment, the defervescence is prompt but the patient may relapse and usually the relapse occurs about eight days after the antibiotic has been stopped. One would surmise that had antibiotic treatment been extended recrudescence might have been prevented. Under situation C are the results of a human experimental trial conducted by the United States Army typhus team in Malaya under the general direction of Dr. Joseph E. Smadel. Human volunteers were infected with the agent of scrub typhus and given chloramphenicol daily for 28 days. The incubation period of typhus is approximately seven days, the anticipated course of the disease two weeks, and in this trial the antibiotic was given for seven additional days for good measure. The antibiotic is suppressive in its mode of action, so that on stopping the drug, under these conditions, active signs of full blown disease develop in most instances.

Now consider Situation B, when the antibiotic has been administered on an intermittent basis. During the rest periods there may be unapparent disease consisting of moderate headache, low grade fever and rickettsia may be isolated during the treatment interval. Under this regimen of intermittent therapy for about five weeks, there will be clinical suppression of the acute illness and the patient will develop some measure of immunity, at least enough to keep him from developing the active disease.

The studies just cited did demonstrate that the timing of antibiotic treatment exerts some influence upon the rate at which immunity develops. The term "immunity" is used in a broad sense.

(Slide) One final slide. Colonel William Tigertt reported this work on Q fever at the May 1956 meeting of the Association of American Physicians.

A trial using Rickettsia burneti or the agent of Q fever was conducted in human volunteers. It may be seen that as the infecting dose was increased the incubation period became shorter. Moreover, as the infecting dose increased, more of the subjects developed detectable clinical disease as well as serologic evidence for the presence of disease.

It is of interest that the antibiotics influence the course of patients with Q fever, similar to that in scrub typhus. In this study, when these infected subjects were given Terramycin within the first or second day of the active disease, subsequent relapse did not occur. This differs from the comparable situation in scrub typhus. However, when the antibiotic was given soon after infection, the antibiotic merely prolonged the incubation period. Such subjects treated with the antibiotic for five days beginning immediately after administration of the infecting dose, ultimately developed the disease.

One additional point is of considerable interest. The administration of killed Q fever rickettsia soon after the administration of viable Q fever rickettsia was sufficient in some instances to keep the patient from developing active disease. In other words, some volunteers developed resistance from the killed microorganisms before the incubation period of the viable organisms had been spent.

In summary, we may conclude that as far as the practical management of the rickettsial infections is concerned, the antibiotic drugs are amazingly effective. In the late case, it is not sufficient to make a diagnosis of rickettsial infection and prescribe an antibiotic. It is necessary to provide adequate circulatory support. These tissue changes provide a challenge in the rickettsial diseases. It is necessary to define the changes within endothelial cells and to determine why the capillaries are so permeable. Knowledge of the alterations at the tissue level is needed for more comprehensive management of the seriously ill late patient.

MODERATOR ROGERS: Thank you, Dr. Woodward.

Microorganisms in the psittacosis ornithosis group have now been reclassified as rickettsiae. Is there any clinical way we can differentiate specific rickettsial pneumonia from viral "atypical" pneumonia, Dr. Kilbourne?

DR. KILBOURNE: It may be possible to do so, but I can't. We have been fooled even in New York City with patients in whom we had no reason, on epidemiological grounds, to suspect psittacosis infection. We have treated them as atypical pneumonia, meaning we do nothing for them, and then have been astounded retrospectively to find they have developed complement fixing antibodies against psittacosis agents. I think there are some points, however, that might be helpful. Certainly most cases of psittacosis with pneumonic involvement are more severe

infections than most cases of the nebulous entity that we call atypical pneumonia, which is almost unquestionably a number of entities of probable viral etiology. I believe psittacosis infections differ principally in that they tend to be more acute, more precipitous in onset. They are, in my experience, almost invariably attended by rather racking headache and severe constitutional reaction. These signs may be seen at times in the virus sort of atypical pneumonia but not in most cases, and usually the chief helpful distinguishing feature on clinical grounds is the rather protracted and indolent course of atypical pneumonia of virus etiology. The onset tends to occur very gradually after preceding upper respiratory tract signs. In my experience the onset of psittacosis is more rapid.

MODERATOR ROGERS: *Do you thus treat very sick patients with a viral-like pneumonia as if they had psittacosis?*

DR. KILBOURNE: I usually do, for the further reason that I think, though we speak much of atypical pneumonia as being a virus disease and whether or not we question the efficacy of broad-spectrum antibiotics in its management, there is a theoretical basis for assuming that at least part of the severe illness is related to possible concurrent or intercurrent bacterial infection. The pathology of the disease is accompanied by bronchiolar excavation. The fatal cases always show some evidence of bacterial infection. So I think on this ground as well as on the basis of the very great difficulty in distinguishing, at least in my mind, the syndrome from psittacosis, that it certainly would be proper to treat with antibiotics.

MODERATOR ROGERS: *What antimicrobials do you use?*

DR. KILBOURNE: I believe it probably is analogous to the rickettsial situation in that it does not matter a great deal which one is used. I have had more experience with oxytetracycline than anything else and this has proved efficacious,—a gram a day is usually sufficient. However, it seems to be necessary to continue treatment for at least three weeks if febrile relapse is to be avoided. This again is on the basis of very slight experience but with cases authenticated by laboratory documentation.

MODERATOR ROGERS: *Are there any other viral diseases that respond to specific antimicrobial therapy? Again, Dr. Kilbourne, is there anything this audience should know about the management of the common cold or influenza?*

DR. KILBOURNE: By the very nature of our definitions these days I believe all viruses which are not responsive to the present day antimicrobial agents can be excluded automatically from consideration in discussions of this sort. As a matter of fact, the impetus for reclassifying the larger viruses of the psittacosis group arose largely from the fact that they respond to antimicrobial agents. So the sad fact remains that we do not have any specific chemotherapy or antimicrobial therapy available for the smaller viruses.

Just a brief word about the use of antimicrobial agents or antibiotic agents in such virus diseases as influenza of the present day [1956 —not the Asiatic Type A variant Influenza of 1957.—Ed.] and that is that I believe the use of these agents is definitely not indicated unless one is dealing with older people or people in whom pulmonary complications might be anticipated. The few people who die in the course of influenza epidemics are usually in the older age groups of the population or are those with previous lung disease of some sort.

We had practical experience with this in a large scale outbreak in Fort Monmouth in 1947. There we had the problem of deciding whether to treat everybody with prophylactic antibiotic therapy or whether to treat nobody. Because of the shortage of medical officers we were concerned about not using antimicrobial prophylaxis, but nevertheless we decided to follow this course and found that in this group of young, previously healthy adults, that we had no trouble. There were some bacterial complications but I think this was an experience which has been supported by a number of other studies. My belief is then, that in general there is no indication,—with the possible exception of measles in children which is severe,—for the use of antimicrobial therapy with the virus diseases caused by the smaller viruses.

MODERATOR ROGERS: *Dr. Chaves, we have kept you very quiet. We want to consider briefly the therapy of tuberculosis and learn of any recent changes in the management of this disease. Is tuberculosis a vanishing disease? Are you seeing less tuberculosis here in New York City than heretofore?*

DR. CHAVES: Basically we are still seeing such large numbers of people with active tuberculosis and recent tuberculosis that from a practical point of view the answer is, it is still very much with us.

MODERATOR ROGERS: *How are you handling new cases of minimal tuberculosis at this time, Dr. Chaves?*

DR. CHAVES: If the cases are minimal and active, the chances are one is faced with the problem of what to do in individuals whose diagnoses still have not been confirmed bacteriologically. If we assume that there is roentgenographic evidence of an infiltrate which is believed to be of recent origin and looks like tuberculosis in an individual whose tuberculin test is positive, the chances are there will not be bacterial confirmation in such a case for at least six to eight weeks, even if one is eventually forthcoming. In such an instance I feel one should always keep in the back of one's mind the possibility that another disease may be the cause of the x-ray lesion, but it is perfectly reasonable to proceed to treat this patient with drugs.

MODERATOR ROGERS: *What drugs?*

DR. CHAVES: I would treat such a patient with a combination of isoniazid and p-amino salicylic acid.

MODERATOR ROGERS: *Would you put this patient to bed? Is bed rest still considered necessary for patients with proven minimal tuberculosis?*

DR. CHAVES: I would not put such a patient to bed. I don't believe it is necessary. In some instances I might even permit such a patient to continue on the job, provided the job is a good one and one which the patient can carry out without too much physical activity.

MODERATOR ROGERS: *That is a startling statement.*

DR. CHAVES: On the other hand, in some instances I would even insist that the patient go to a hospital because I would feel that a regimen of decreased activity that this disease requires could only be carried out outside of the patient's home environment. In other words, the indication for hospitalization of minimal tuberculosis is mainly a social one and is a matter for individualization.

MODERATOR ROGERS: *Dr. Woodward, I see you grinning here. How about Baltimore, how do you handle tuberculosis there? Do you put such patients to bed?*

DR. WOODWARD: I was grinning because I did not have to answer that question. Has there not been a study reported in this country with consideration given to the relative merits of ambulation versus bed rest? I would say that in Baltimore we are inclined to be conservative and advocate bed rest.

MODERATOR ROGERS: *Dr. Tompsett, would you care to comment on this?*

DR. TOMPSETT: Dr. Chaves knows so much more about this. I would like to agree with him. I don't have the experience but I certainly think that if this procedure is not followed now, it is something we shall be doing very soon.

MODERATOR ROGERS: *Dr. Chaves, I gather you hospitalize some patients with minimal tuberculosis whereas others you are content to treat on an ambulatory basis. What decides this for you?*

DR. CHAVES: For example, right now I am rather heavily involved in a community survey in the Bedford area of Brooklyn where we are picking up on the average about seven or eight active cases of tuberculosis per week, of which approximately 25 per cent are minimal. A number of minimal active cases from this source are referred to a local clinic for treatment where they are permitted to remain on the job or to continue their work as housewives, as the case may be. This has been done after a careful social history indicated that the home situation would permit reasonable cooperation on the part of the patient. But in most instances, in the population group that we are dealing with here, we have recommended, and have been successful in getting the patient with active minimal tuberculosis to go to a hospital because of inadequate home conditions, or a temperament or personality which we believed was not compatible with good control from the clinic.

MODERATOR ROGERS: *How about the practitioner who makes the discovery of active minimal tuberculosis, and proves it, in his private practice? Is this a disease which he should treat or should he refer it to someone with special training in tuberculosis?*

DR. CHAVES: The way you phrase the question, there is no doubt that the general practitioner can handle it because you have already handed him a proven case of minimal active tuberculosis. In other words, once a diagnosis has been established I think the management should be rather straightforward, namely, curtailing activity, continuing to check the sputum or gastric contents of the patient at regular intervals, periodic x-ray examination to follow the progress of the disease and long term chemotherapy.

MODERATOR ROGERS: *Let us be more specific—what is long term therapy?*

DR. CHAVES: For minimal active disease I would say at least one year. I have been tending to keep patients with minimal disease on treatment now for about 18 months.

MODERATOR ROGERS: *I notice again you advocate combined therapy. There has been much discussion about the use of more than one antituberculosis agent in minimal disease. What are your reasons for putting these patients on both isoniazid and p-amino salicylic acid and do you use streptomycin in the situation, or do you withhold it?*

DR. CHAVES: Actually, for minimal disease there is not nearly as good a case for combined therapy as there is for more advanced disease with cavitation. Isoniazid, whether it is combined with another drug or not, is quite adequate to take care of most patients with minimal tuberculosis. The reason I advocate the combination of isoniazid and p-amino salicylic acid is because in the more serious forms of disease, it has proven to be a better combination. Therefore I feel that it may be better medicine for a particularly stubborn type of minimal active disease.

MODERATOR ROGERS: *What about the more advanced disease? You mentioned combined therapy has proven superior. Is that because of the development of isoniazid resistance?*

DR. CHAVES: In the first place, there are three important drugs which are combined in various ways, for antituberculosis treatment. The three drugs are streptomycin, p-amino salicylic acid and isoniazid. They can be combined in any way: isoniazid and p-amino salicylic acid; isoniazid and streptomycin; streptomycin and PAS; or all three drugs can be used together. One can argue for any combination. One can argue against any combination. Would you want me to go through all those possibilities, or what?

MODERATOR ROGERS: *Is there any one "best" combination?*

DR. CHAVES: I think all of those combinations have their points. I personally believe that isoniazid, being the best of the three drugs, should be used when one has a fresh case of tuberculosis because it seems to me when a disease like tuberculosis is treated for the first time, one should use his best ammunition right off the bat, rather than saving it for some future emergency which may never show up.

MODERATOR ROGERS: *I would like to throw two more tough questions to you and then I will let you off the hook. What about the management of tuberculin converters? There has been much discussion about treating young children who convert from a negative to a positive tuberculin test, because we have highly effective therapy in isoniazid. What is your feeling on this?*

DR. CHAVES: This is a field that is full of controversy, as you know.

I think there is general agreement that when the tuberculin reaction of a child under the age of three converts, that child should be treated with isoniazid, either alone or in combination with PAS because the incidence of disseminated form of tuberculosis is so high in this age group.

MODERATOR ROGERS: *How high is it in this group?*

DR. CHAVES: It varies with the age. It falls right from birth but I would say that one may expect disseminated disease to occur in approximately 5 to 10 per cent of the converters under one year of age, and less frequently in the two and three year age group. But that is a significantly high percentage and it therefore seems worth while to treat all such children with isoniazid at the time of conversion.

As far as the treatment of converters in other age groups is concerned, I don't really think it merits much consideration. The arguments in favor are theoretical and speculative.

MODERATOR ROGERS: *I gather that when a medical student converts with no evidence of active disease you are inclined to withhold antibiotics.*

DR. CHAVES: I personally would treat them but I have been involved in some rather long arguments on that. As I said before I don't really believe there is conclusive evidence one way or another. If you believe there is a 1 per cent chance that a medical student who converts his tuberculin reaction might come down with significant pulmonary disease, by that I mean x-ray evidence of a lesion, and if you could prevent that by giving isoniazid, it is worth treating all 100 converters to save the one medical student coming down with the disease. The question is, can you do that? That has not really been shown.

MODERATOR ROGERS: *Just one more question: What is the status of BCG vaccination?*

DR. CHAVES: I think the questions you are asking are clear in my mind but because of widespread controversy I will give only my point of view. It is too bad we do not have another panelist with a contrary point of view! I believe the answer to the question as to the advisability of BCG vaccination is much easier now than it was a year ago, because there has been an excellent control study, by the British Medical Research Council in England, on the use of BCG which, to my way of thinking pretty convincingly shows that BCG has definite protective value against tuberculosis in adolescents. I say in adolescents because

that is the only age group that was studied. I think there is agreement that it has some value. The real question is, *how much* protection does BCG give the individual and is the amount of protection obtained worth the risks involved in vaccinating and the loss of the tuberculin test for diagnostic purposes.

In a nutshell, again, in areas where there is a lot of tuberculosis, BCG has a very definite place and where there is a small amount of tuberculosis it does not offer enough to warrant using it on a large scale.

MODERATOR ROGERS: *Very good! Thank you, Dr. Chaves!*

Would anyone else on the panel care to take issue with any of Dr. Chaves' carefully phrased answers? If not, we have some good questions here and I would like to make use of some of them. Dr. Woodward, what is the incidence of serious reactions to chloramphenicol?

DR. WOODWARD: I think the precautions that one takes with chloramphenicol are the precautions to be considered with most drugs. This question presumably refers to the blood dyscrasia problem. We have treated approximately 1600 patients with various specific infectious diseases. Blood counts were performed, before, during and after the administration of chloramphenicol for the *specific* illness. The antibiotic was given to typhoid fever patients with leukopenia of 1500 white blood cells per cu. mm. and to other patients with anemia of varying degree resulting from the specific disease. We have not encountered blood dyscrasias.

More recently at the Antibiotic Symposium in Washington, a paper described the results of long term chloramphenicol therapy in 2100 patients. Blood dyscrasias did not occur. I believe that chloramphenicol has caused blood dyscrasia in certain reported instances but seriously doubt that the true incidence is known. The hazard for important blood dyscrasia must be quite low when one considers the wide range of exposure to this antibiotic and the relatively small number of reported cases.

MODERATOR ROGERS: *You feel when you have specific indications like the diseases you have been discussing–*

DR. WOODWARD: I would give the antibiotic when specifically indicated. We do not withhold chloramphenicol. We prescribe it freely.

MODERATOR ROGERS: *Dr. Tompsett, I direct this one to you: How do you manage both urinary tract infections and more serious bac-*

teremic infections due to E. coli?

DR. TOMPSETT: It is somewhat unpredictable as to which drug is going to work. In such a case one has to rely on the sensitivity test, either the patient's response or *in vitro* sensitivity tests. By and large I feel that for a bona fide pyelonephritis due to E. coli, we would start the patient on tetracycline and follow through as is indicated thereafter. But there are several drugs which may be valuable in addition to tetracycline. The sulfonamide drugs of course are very valuable as is chloramphenicol. We generally reserve streptomycin for those persons who have bacteremic disease and who are more severely ill. In those patients we would sometimes use streptomycin.

MODERATOR ROGERS: *Is it your usual practice to start with tetracycline or sulfonamides, making subsequent changes on the basis of sensitivity studies or the patient's response?*

DR. TOMPSETT: The latter may be clearer and faster than the sensitivity test.

MODERATOR ROGERS: *Is it advisable to give B complex vitamins when using broad-spectrum antibiotics? Dr. Kilbourne, would you take a crack at that? Do you feel it is necessary?*

DR. KILBOURNE: I do not. There is some evidence which suggests that actual B complex deficiency can develop with long term antimicrobial therapy. I think that with our current methods nutritionists have difficulty detecting subclinical or borderline nutritional states so it is difficult to say that short term therapy has caused any important problem. My feeling would be that there is certainly no evidence for giving B complex except during the protracted administration of antimicrobials, particularly of the broad-spectrum variety.

MODERATOR ROGERS: *Would anybody argue with that? Dr. Woodward? Dr. Tompsett?*

We have time for just one more question: Is there any use in giving antihistamines with penicillin to prevent serious reactions? There is an addendum: How do you treat a severe penicillin reaction when it occurs in the physician's office or the patient's home?

Dr. Tompsett, do you think antihistamines are of any value in protecting the patient with a history of a previous penicillin reaction?

DR. TOMPSETT: I could answer that by saying, if the patient gives a history of previous reaction we don't like to use penicillin unless it is absolutely necessary. We avoid it then, when possible. If the patient

gives a history of reaction, however, and we feel that penicillin is required, we don't ordinarily give antihistamines until the patient again develops hypersensitivity, in which case we would. In other words, I don't think this should be done routinely. They are very useful in mild allergic reactions to penicillin.

MODERATOR ROGERS: *Dr. Kilbourne!*

DR. KILBOURNE: Antihistamines are not very helpful in drug fever and more important manifestations.

DR. TOMPSETT: I would say more than that! They are practically useless in patients with drug fever.

MODERATOR ROGERS: *The remainder of the question is: How do you treat a severe penicillin reaction when it occurs?*

DR. TOMPSETT: I think the main drug is epinephrine in severe allergic reactions. This can be followed by the use of Benadryl for carrying the patient along after this, but usually by the time one gets through giving the patient epinephrine, intramuscularly or at times intravenously—I am now talking about anaphylactic shock—the issue has been pretty well decided. Fairly general supportive measures may then be enough. I am not sure that we do much of value beyond the administration of epinephrine.

MODERATOR ROGERS: *In other words, you would try to avoid this situation whenever possible. I certainly agree that when anaphylaxis occurs treatment may be of very little moment.*

We have come to the end of our time. I would like to thank all the panelists and our audience for participating in the discussion this afternoon.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

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A Study of Hemosiderosis with the Aid of Electron Microscopy

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Hemosiderosis has been studied for a long time, but the ultrastructure of hemosiderin remains to be elucidated. It is known that there is a close relationship between the iron storage compound, ferritin, and hemosiderin, previous work by others having indicated that the ferric hydroxide micelles of both compounds are similar, while the organic components appear to be different.[1-3] In 1954 Farrant[4] showed by means of electron microscopy that the ferritin molecule contains a core of closely adjoining, electron-dense particles (commonly four), representing the iron micelles, and a peripheral shell that is not dense to electrons and presumably represents the protein component, apoferritin. Later, Novikoff, Beaufay and de Duve[5] and Palade and Siekevitz[6] suggested that certain electron-dense particles, present in cells of normal rat livers and spleens, might represent the iron micelles of ferritin molecules, though the substructure discovered by Farrant was not evident at the resolutions obtained.

Using electron and light microscopy, the author has studied the fine structure and disposition of hemosiderin and ferritin in several types of cells from rats with early experimental hemosiderosis, and from human patients. Typical, isotropic, iron-positive hemosiderin granules were found to contain innumerable closely packed, electron-dense particles, embedded in matter that was much less dense to electrons. Similar dense particles were often scattered diffusely through the cytoplasmic matrix. In cells of the proximal convoluted tubules of rats given repeated intraperitoneal injections of rat hemoglobin, the discrete particles had a mean diameter of 55Å, and a size-frequency distribution indicating uniformity. Electron micrographs taken at high resolution have revealed substructure in these particles, commonly in the form of quadruplets of particles with diameters of about 30 Å, and corresponding to the iron micelles of ferritin molecules discovered by Farrant. In *some* of the aggregates ("hemosiderin granules") in these cells, a molecular lattice structure identical with that of crystalline rat ferritin was present. However, most of the aggregates in these cells did not display crystalline structure. Electron diffraction studies on aggregates in cells, and on crystalline ferritin, have confirmed the inference that the dense particles are iron hydroxide micelles. Many of the aggregates were situated within discrete cytoplasmic bodies, delimited by double membranes and containing "cristae", thus resembling mitochondria. Often the membranous borders of these bodies were disrupted, and the bodies seemed to be discharging particles into the surrounding cytoplasmic matrix. The term "siderosomes" is proposed for these specialized bodies which appear to be derived from mitochondria, and to participate in the metabolism of ferritin. The findings on hemo-

siderin-laden macrophages and fixed reticuloendothelial cells from these rats were similar, although "siderosomes" were not so numerous in these cells.

Hemosiderin granules in hepatic parenchymal and reticuloendothelial cells of rats that had been given a diet containing 0.75 per cent dl-ethionine during a period of two months contained similar electron-dense particles; many of these had diameters of 50 to 60 Å. Similar particles were scattered through the cytoplasmic matrix. The structure of the particles in these cells varied, but many were composed of typical quadruplets. Siderosomes with peripheral double membrances, and occasionally with internal cristae, were abundant.

In further work specimens obtained at an operation from the liver and spleen of a patient with advanced transfusional hemosiderosis were studied. In hepatic parenchymal cells, in fixed reticuloendothelial cells and macrophages, many similar electron-dense particles were found, scattered and in aggregates. Although there was considerable variation in particle sizes, the typical molecular substructure of ferritin iron micelles was again demonstrable in many particles. Statistical studies of measurements of the particle sizes have demonstrated a definite periodicity which indicates that there is a fundamental unit iron micelle that is smaller than those demonstrated thus far. The larger micelles appear to be integral multiples of this unit. Siderosomes were quite scarce in this material, and this may reflect the long duration of the hemosiderosis.

The findings indicate:

1. That the iron micelles of hemosiderin and ferritin contain similar molecular subunits, and are at times indistinguishable, but that in hemosiderin the state of aggregation of the sub-units is quite variable.

2. That *some* hemosiderin granules, visible with light microscopes, and occurring early in the course of experimental hemosiderosis, are crystals of ferritin.

3. That there is a unit micelle that is smaller than any yet seen with electron microscopes of which the larger micelles are whole number multiples.

4. That hemosiderin and ferritin aggregates are often situated within discrete cytoplasmic organelles, particularly in early hemosiderosis.

5. That these organelles appear to be derived from mitochondria.

6. That hemosiderin and ferritin may be either synthesized or concentrated within these bodies, and later discharged into the cytoplasmic matrix.

DISCUSSION

S. GRANICK: The paper of Dr. Richter is interesting to me for two reasons: first, I think it may tell us about ferritin synthesis; second, it may indicate an intermediate stage in hemosiderin formation towards hemochromatosis.

Before I discuss ferritin synthesis, I should like very briefly to review some of the properties of ferritin. It consists of a colorless protein molecule, apoferritin, which has a molecular weight of about 500,000. The apoferritin has four holes in it, which can be partially or completely filled with brown colored ferric hydroxide. Ferritin signifies apoferritin plus ferric hydroxide. Each hole in the protein may contain up to 1000 FeOOH units, all linked together to form a micelle. The FeOOH may make up 36 per cent of the dry weight of the ferritin. The FeOOH has a special magnetic susceptibility of three unpaired electrons per iron atom. Most other iron compounds have either one or five unpaired electrons per iron atom. The crystals of ferritin are brown. One may dissolve out the iron hydroxide micelles within the ferritin molecules by means of reducing agents such as cysteine, glutathione or hydrosulfite, and one may then prepare colorless apoferritin crystals, devoid of the iron hydroxide. An early photograph of ferritin molecules with the electron microscope, prepared by Dr. Keith Porter, shows the considerable variation in the amount of iron hydroxide observed in different ferritin molecules.

The function of ferritin is to serve as a storage form, not only of iron, but of protein as well. When an animal is bled, ferritin of the liver breaks down to release the iron; the protein portion also breaks down to amino acids. So the bone marrow is not

only supplied with iron, but also with amino acids due in part to the mobilization by breakdown of ferritin of the liver.

Dr. Richter's findings are especially interesting in what they may signify about the synthesis of ferritin. The present story of the synthesis of ferritin may be summarized thus: There is always a small concentration of apoferritin in many tissues. When iron is supplied to tissues like the intestinal mucosa or liver, the apoferritin increases over four-fold in a few hours, and the iron, probably in the form of ferrous bicarbonate, oxidizes and attaches to the apoferritin. The synthesis and breakdown of ferritin, i.e., its turnover, appear to be very rapid. The addition of iron to a liver cell causes an increase in this protein, and in no other protein, so the reaction is specific, as noted by the studies of Fineberg and Greenberg.[7] It has intrigued a number of investigators interested in protein synthesis to study this particular protein, because if iron is administered the protein concentration goes up rapidly.

Studies with labelled iron and labelled leucine by Loftfield and Bonnichsen[8] suggest that liver ferritin arises in two distinct places. They found newly formed ferritin in a soluble fraction, and in a microsomal fraction. According to these workers ferritin is first most rapidly labelled in the soluble fraction not connected with the microsomes. For a clear interpretation I think we must wait for further experiments, since most indications of protein synthesis suggest that protein is synthesized in connection with the endoplasmic reticulum (i.e., the microsomal portion).

The findings of Dr. Richter suggest that ferritin is present in mitochondria; however, his experiments extended over a period of days instead of hours so one must consider the time factor in relation to iron deposition and localization. Some of the intriguing questions raised by Dr. Richter's findings are the following:

1. Are ferritin molecules produced by mitochondria or do the mitochondria have a mechanism for specifically storing them? 2. Or is apoferritin (but not ferritin) produced or accumulated in the mitochondria? If apoferritin were in the mitochondria it is conceivable that soluble ferrous bicarbonate might enter and be rapidly oxidized in the mitochondria to the insoluble ferric hydroxide which would deposit in the ferritin molecules. Because of the oxidative enzymes in mitochondria, ferric oxide might accumulate there.

Next let us consider the significance of Dr. Richter's findings as related to hemosiderin and to hemochromatosis. It has long been recognized that hemosiderin is a loose term to designate granules which contain iron that are visible in the light microscope. Some of these hemosiderin granules may well represent the kind Dr. Richter has found, which are modified mitochondria filled with ferritin molecules. It is probably from such granules that investigators like Greenberg and Fineberg were able to isolate some ferritin.

Perhaps in hemochromatosis, when cells are damaged, not only do the mitochondria break down, but the iron may be released from them in such amounts as to damage the cells still further and perhaps irreversibly.

Are all iron granules of this kind? Probably not. One may isolate some iron granules from horse spleen that have a composition of almost pure FeOOH. To explain their origin one might postulate that denaturation of ferritin has led to the stripping off of the protein so that only FeOOH micelles remain, which then aggregate into these granules of almost pure FeOOH.

There are other iron staining granules which may represent denatured globin with adsorbed iron oxide. Such granules are seen in the intermediate stages of the breakdown of red cell fragments by phagocytes.

It is also probable that saccharated iron which it taken up by phagocytes very rapidly is not represented by the Richter granules, but that the iron may then become distributed to the mitochondria more slowly.

Other iron granules which might be worth while for examination with the electron microscope are those in the sideroblasts and siderocytes, granules which are formed in immature red cells and might be similar to Richter granules.

In conclusion, it would seem to me that the Richter granules could serve as a device

to store large amounts of iron when iron becomes excessive, or where iron could be accumulated slowly and be used, as in the immature red cells, for the manufacture of hemoglobin. So instead of having the ferritin diffusely scattered and very rapidly available, the ferritin might be compartmentally separated from the rest of the cell and more slowly released.

Furthermore, it seems to me that Dr. Richter's work is important for it suggests that mitochondria are involved in iron storage, and perhaps in apoferritin synthesis. This would mean that the metabolism of mitochondria might be intimately connected with the regulation of iron movement into and out of cells.

Dr. Richter is to be congratulated for his fine technical skill and perseverance in obtaining these excellent electron microscope pictures, which are at present at just about the limit of resolution of the electron microscope.

ALFRED ANGRIST: I wonder whether the association of mitochondria with respiration and the known association of the iron ion with oxidative enzymes has any possible relationship to the localization so beautifully demonstrated by the accumulation of the hemosiderin particles in the mitochondria.

SIGMUND L. WILENS: I would like to ask whether you were able to study the structure of the iron granules in cells of the reticuloendothelial system, such as the Kupffer cells of the liver and the reticulum cells of the spleen. Do such cells actually contain mitochondria, and if they do, is the relationship of the pigment granules to these structures the same as in liver cells and renal tubular cells?

GOETZ W. RICHTER: In answer to Dr. Angrist's question, I must confess my ignorance; perhaps Dr. Granick could answer it. Actually I do not think the relationship between oxidizing enzymes and ferritin synthesis is known.

So far as the structure of hemosiderin in the reticuloendothelial system is concerned, it is exactly the same as in the liver and kidney cells. I have shown a picture of hemosiderin and ferritin in a macrophage from the spleen in a case of hemosiderosis. It matters during what stage of hemosiderosis the material is obtained, but in the experimental rats the structure of the iron micelles in reticuloendothelial cells, liver and kidney cells, was the same. For technical reasons the demonstration of the relationship between hemosiderin and the siderosomes was more easily accomplished with material from the kidney and from the liver.

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Observations with the Electron Microscope on the Lucké Renal Adenocarcinoma

(Abstract)

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The renal adenocarcinoma of the frog described by Lucké (1934) occurs in 2 to 4 per cent of frogs of the species *Rana pipiens* collected in northern New England. The tumor shows intranuclear inclusion bodies and it can be transmitted by cell-free filtrates to animals of the susceptible race, but not to others. Lucké concluded from these observations that the tumor is probably caused by a species and organ specific virus. Electron micrographs of spontaneous kidney tumors reveal spheroidal cytoplasmic particles of uniform size about 100 $m\mu$ in diameter. They closely resemble particles found in tissues infected with herpes simplex and related viruses. They have a thick capsule enclosing a central cavity that contains an eccentrically-placed, dense, ovoid body. The nuclear inclusions that are seen with the light microscope are found in electron micrographs to be made up of closely packed thin-walled vesicles (100 $m\mu$). These are sometimes precisely arranged in crystalline array, but more commonly are randomly scattered in a fine granular matrix. Dense ovoid bodies are found in close association with certain of these vesicles. In some instances they are entirely within the vesicles, in others they are partly in and partly out, and a considerable number are free in the nucleoplasm. These associations of the dense bodies with the vesicles are tentatively interpreted as developmental stages of virus particles.

A number of other filamentous, vesicular and vacuolar inclusions occur in the nucleus and cytoplasm. These are too diverse for all to be fitted into any hypothetical scheme of virus multiplication and it is believed that some of them may be merely by-products of the reaction of the host cell to a virus.

It is concluded that the distinctive particles described are probably virus particles and that they may be the tumor agent postulated by Lucké. However, the viral nature of the particles has not been proved and a causal relation between them and the formation of the tumors has not been definitely established.

DISCUSSION

JOHN G. KIDD: Dr. Fawcett has provided us with a striking example of what a man can do who first digs in and through years of application becomes an expert cytologist and light microscopist, then transforms himself by dint of further thought and labor into an electron microscopist, and finally, through a series of fortunate incidents and the purposeful and discerning pursuit of curiosity, undergoes a further metamorphosis and becomes an experimental pathologist. I am sure we can all take pleasure in his final flowering and welcome him into the fold.

Dr. Fawcett's observations are so explicit and his interpretations so closely reasoned that I do not see how anyone can find anything to quarrel with him about, or to criticize in relation to his position. His is certainly the most convincing demonstration thus far of particulate and distinctive bodies in naturally occurring cancer cells. When the electron microscope first became available, a number of attempts were made—notably by Keith Porter—to find such bod-

ies in the cells of some of the sarcomas of fowls that can be induced with filtrable agents, and in the cells of mammary carcinomas of mice, in which the so-called milk factor is implicated as an etiologic agent. But Dr. Porter's early efforts in this direction were made before he had perfected the methods of fixation and thin-sectioning which stand as a monument to his perseverance and skill and which have indeed made present day electron microscopy feasible; for this reason and others perhaps his pictures of diverse particulate bodies in the cells of these experimental growths were not altogether convincing. A number of subsequent workers—Dr. Fawcett excepted—even though they have had the benefit of the newer techniques and with more advanced knowledge of the normal constituents of tissue cells that are resolvable by means of electron microscopy, have also fared poorly in their attempts to disclose distinctive morphologic forms in cancer cells by means of electron microscopy. Now Dr. Fawcett has achieved this, and his findings have wide implications.

Dr. Lucké was one of my friends, and I remember well his initial discovery of the renal carcinomas of frogs, and the extraordinary difficulty that he faced in studying the relationship between the nuclear inclusions, which he saw in the carcinoma cells and which indicated to him the possible presence and activity of a virus, and the effects of glycerinated extracts of the cancers which he injected into normal frogs with a view to inducing renal cancers in them. For many of the extracts were essentially devoid of effect while others seemed to induce renal carcinomas in 17 to 20 per cent of the frogs into which they were injected, but only after a long interval of time—six months or more. These facts have long been puzzling, and they were essentially responsible for Dr. Lucké's cautious interpretation of his results: actually he used the term "probable causation by a virus" in the sub-title of one of his definitive publications. Dr. Fawcett's observations now make it plain that some of the renal carcinomas are composed of cells having many intranuclear inclusions and particulate bodies, while others are made up of cells in which he was unable to find such bodies. Surely it would be of value, as Dr. Fawcett has pointed out in his publications, to test extracts of growths of each sort separately, and compare the results. It is through such experiments that we shall in due course come to know the precise character and functions of the particulate bodies and their relationships to the renal carcinoma cells they inhabit. Furthermore, Dr. Fawcett's observations should encourage other electron microscopists to search further for distinctive bodies in the cells of other experimental tumors, and perhaps also to look for them in the cells of those unusual tumors of human beings—certain gliomas, for example, —in which one can sometimes see inclusions with the light microscope.

As to the nature of the particulate bodies which Dr. Fawcett has demonstrated, it seems to me that much more work will be required before they can without qualification be called viruses. Their morphology alone, although suggestive, does not suffice in my opinion, to define them as such, and we know all too little of their other properties and functions. Even so, I find his observations about the varying forms and situations of the particulate bodies and his "fantastic speculation"—to use his term—that the various forms may represent stages in maturation, at once interesting and stimulating, and not devoid of basis in fact and reason—which is to say meritorious. I am sure he recognizes that in making the speculation, however, he puts himself in a position somewhat comparable to that of a boy, who, having found a number of arrowheads of various sizes on a rocky hillside, arranges them linearly in order of size and suggests to his companions that arrowheads can grow!

VERA B. DOLGOPOL: This remarkable work opens wide the field of investigation of nuclear inclusions that occur in many virus diseases, like chickenpox, herpes, and the "inclusion body disease". Unfortunately, one cannot propagate those viruses at will, and we will have to be content to study occasional material, but the possibilities are immense.

ALFRED ANGRIST: I should like to

ask two questions. The demonstration of the large inclusions with their dense osmophilic background substance, and what seemed like partial preservation of parallel lamellar structure, prompts the first question. Does it have any relation to the Golgi apparatus? The other question is prompted by a finding by Dr. Novikoff in our laboratory. He has noted some evidence of a demonstrable connection between the nuclear membrane and the double-contoured cytoplasmic membrane in some of his tumor cells. I wonder whether Dr. Fawcett has seen the two membranes he has shown so clearly connected in this fashion.

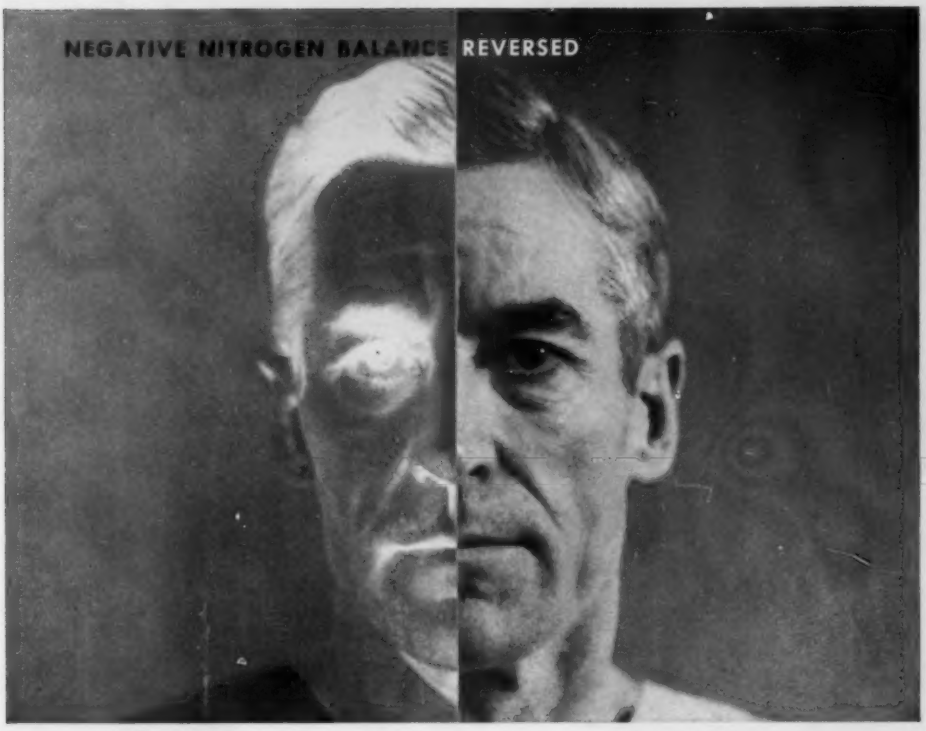
DON W. FAWCETT: In regard to the cytoplasmic inclusions and their possible relationship to the Golgi apparatus: it occurred to us that they might be some abnormality of the Golgi complex; but against this is the fact that, not infrequently, one can see in the same cell one of these vacuolar inclusions and also what appears to be a normal Golgi complex. I think it is unlikely that these inclusions are derived from the Golgi complex, but as yet we have not been able to establish any significant relationship between them, nor between the virus-like particles, and the Golgi complex.

As to the question of the relation of the cell membrane to the nuclear membrane: in the distal convoluted tubule cells of the frog the cell membrane does extend from the base up into the cell to the nucleus or even beyond, and it often comes into very close association with the nuclear membrane, but we have not observed continuity of one with the other in this material.

I would like to emphasize something Dr. Kidd referred to, namely, that there are too many pieces to this jigsaw puzzle and, at present, we cannot put them together into a reasonable picture of virus reproduction without having several unused pieces left over. We believe this work does serve to point out the complexity of the relationship of animal viruses to their host cells, and we hope it will stimulate others who are more competent in the techniques of virology, to undertake the study of this interesting tumor.

SIGMUND L. WILENS: Since the viral-like structures that you have described occur in two distinctive forms, one a vesicle with a double-contoured membrane analogous to a spore, and the other a filament somewhat like mycelia, is there any remote possibility that these structures are in any way analogous to the fungi?

DON W. FAWCETT: I do not know the answer to that. I am not certain that the "filaments" are actually genetically related to the "virus-like particles", even though they always do occur in the same cell. There is no evidence that one develops from the other. I doubt that we are dealing here with a fungus, but I cannot exclude this possibility on the basis of the evidence at hand.



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stimulates protein synthesis,
corrects negative nitrogen balance

Increased nitrogen loss, with resulting negative nitrogen balance, occurs in infection, trauma, major surgery, extensive burns, certain endocrine disorders and starvation and emaciation syndromes. The intrinsic control of protein metabolism is lost and a protein "catabolic state" occurs. A patient requiring more than ten days of bedrest usually has had sufficient metabolic insult[1] to precipitate such a "catabolic" phase.

Nilevar (brand of norethandrolone) has been used in patients with varied conditions including hyperthyroidism, poliomyelitis, aplastic anemia, glomerulonephritis, anorexia nervosa and postoperative protein depletion. The patients gained weight and felt better. It was concluded[2] that "the drug certainly caused a reversal of rather recalcitrant or progressive catabolic patterns of disease."

Nilevar is unique among anabolic steroids in that androgenic side action is minimal or absent.

The suggested adult dosage is three to five tablets (30 to 50 mg.) daily. For children 1.5 mg. per kilogram of weight is recommended.

G. D. Searle & Co., Chicago 80, Illinois.
Research in the Service of Medicine.

---

1. Axelrod, A. E.; Beaton, J. R.; Cannon, P. R., and others: Symposium on Protein Metabolism, New York, The National Vitamin Foundation, Incorporated, (March) 1954, p. 100.

2. Proceedings of a Conference on the Clinical Use of Anabolic Agents, Chicago, Illinois, G. D. Searle & Co., April 9, 1956, pp. 32-35.

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Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

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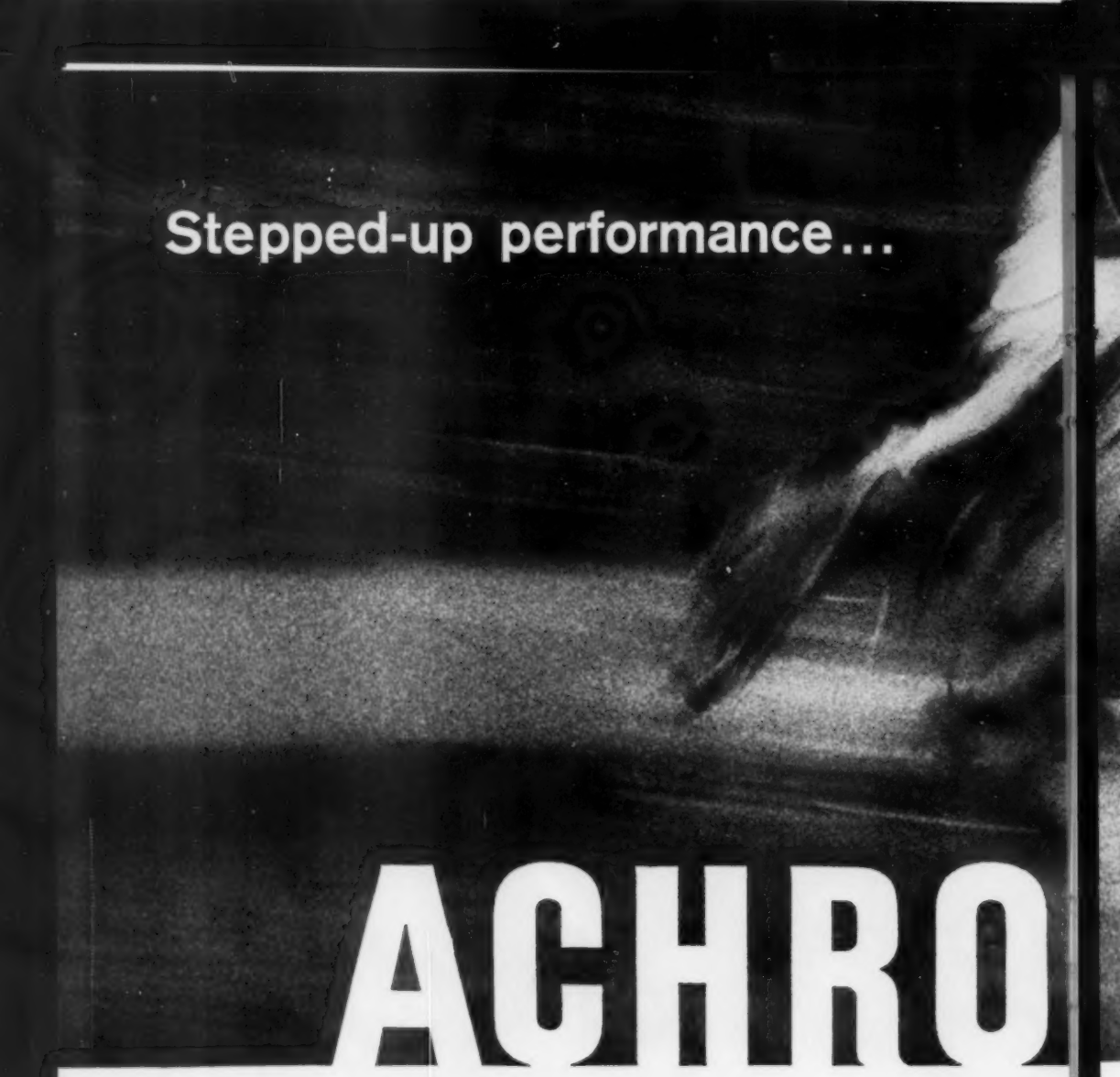

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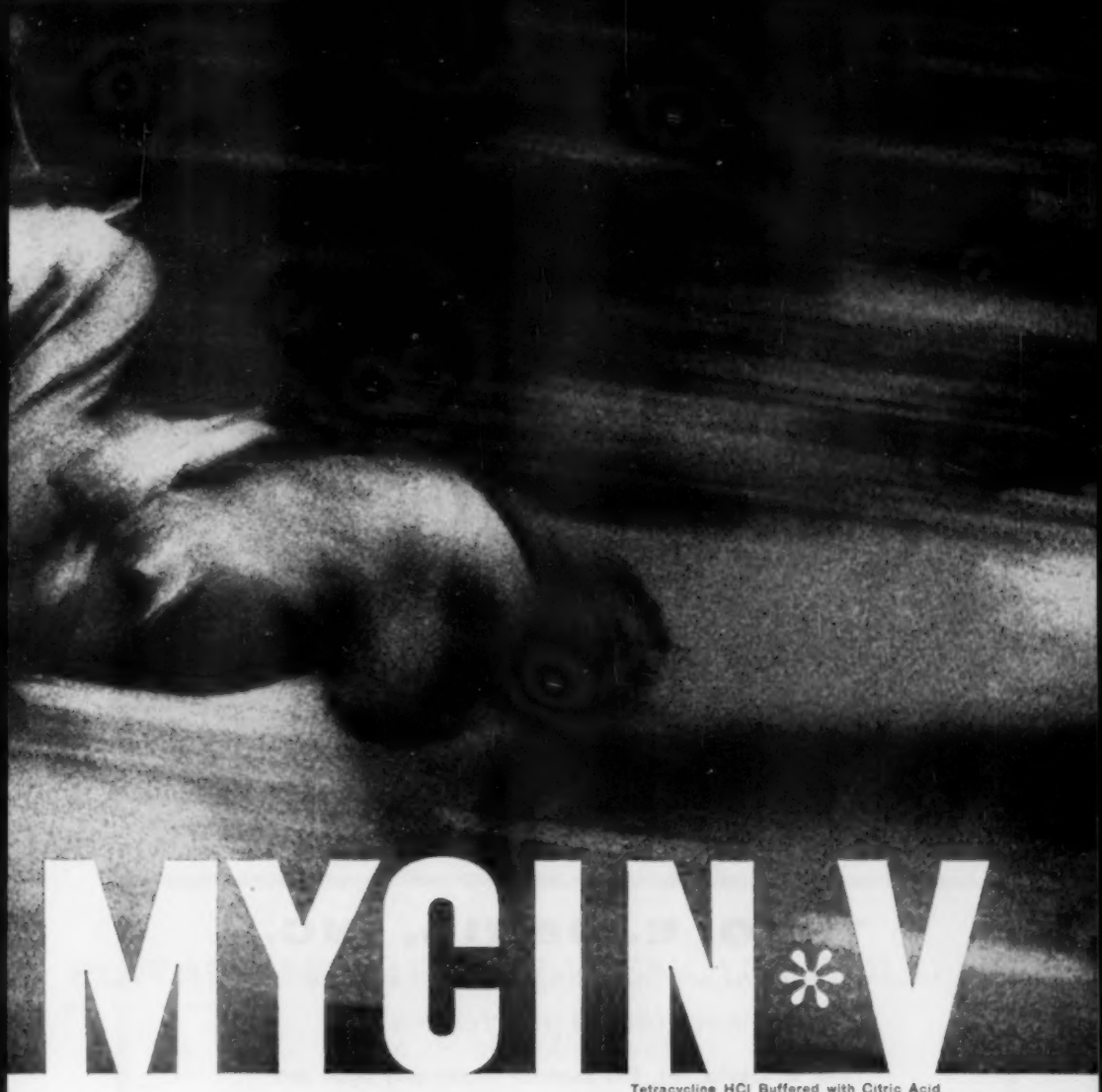

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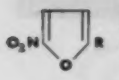

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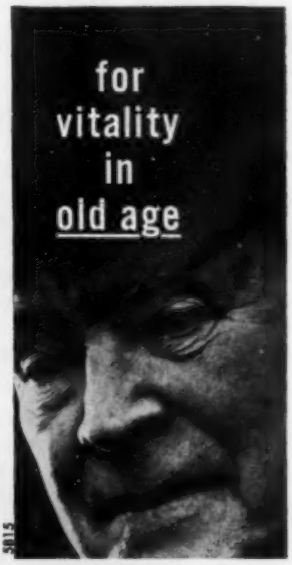

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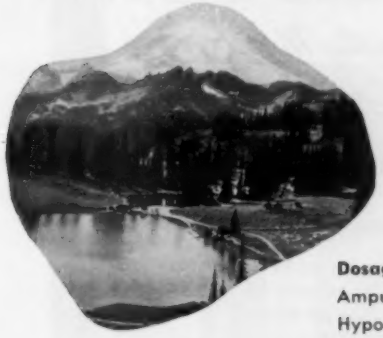

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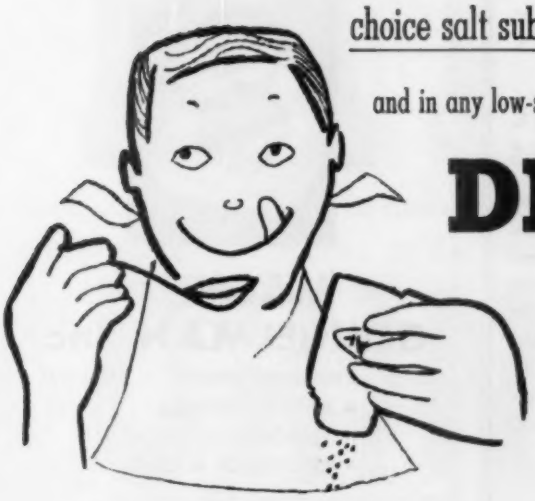

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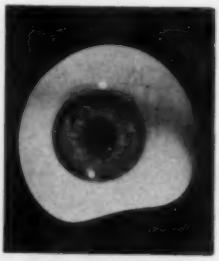

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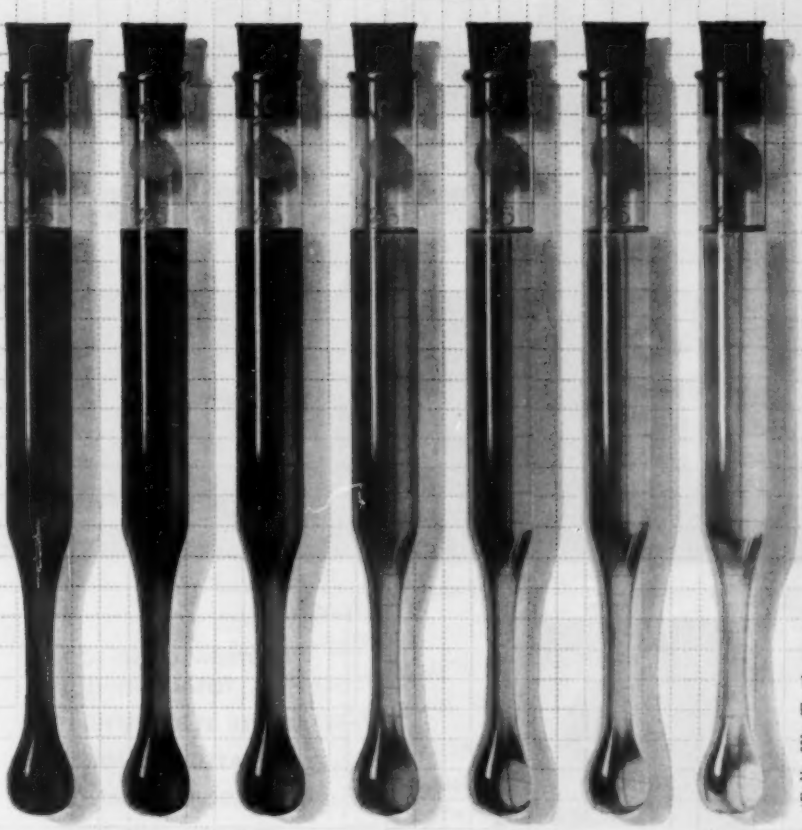

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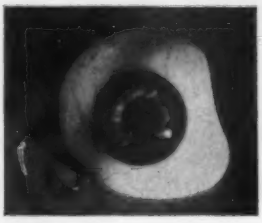

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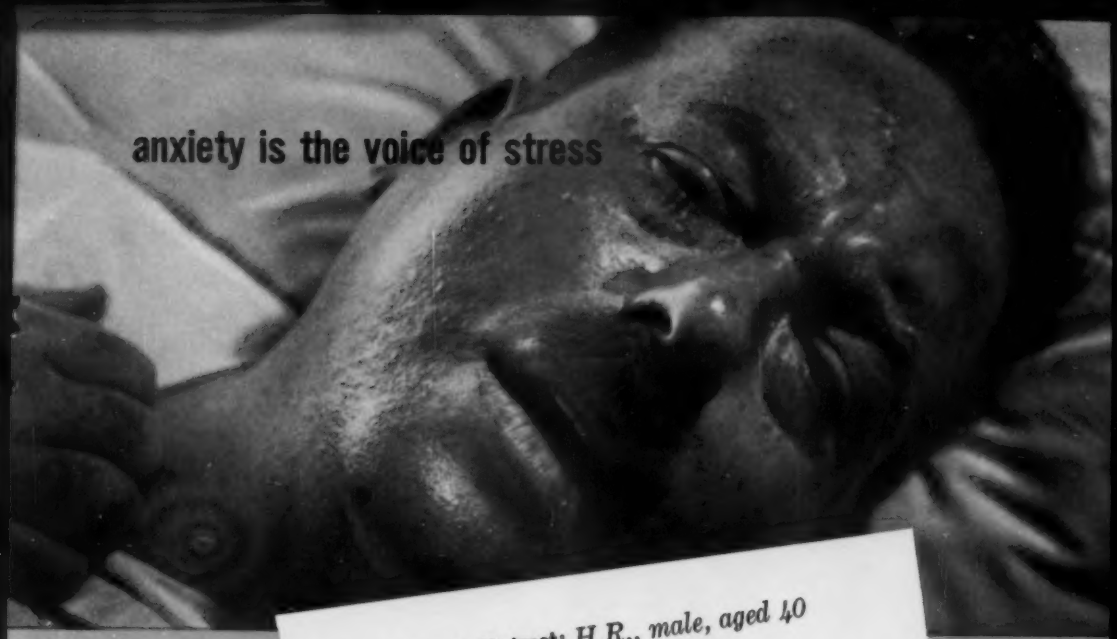

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1. Waldman, S., and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075 (July) 1957.

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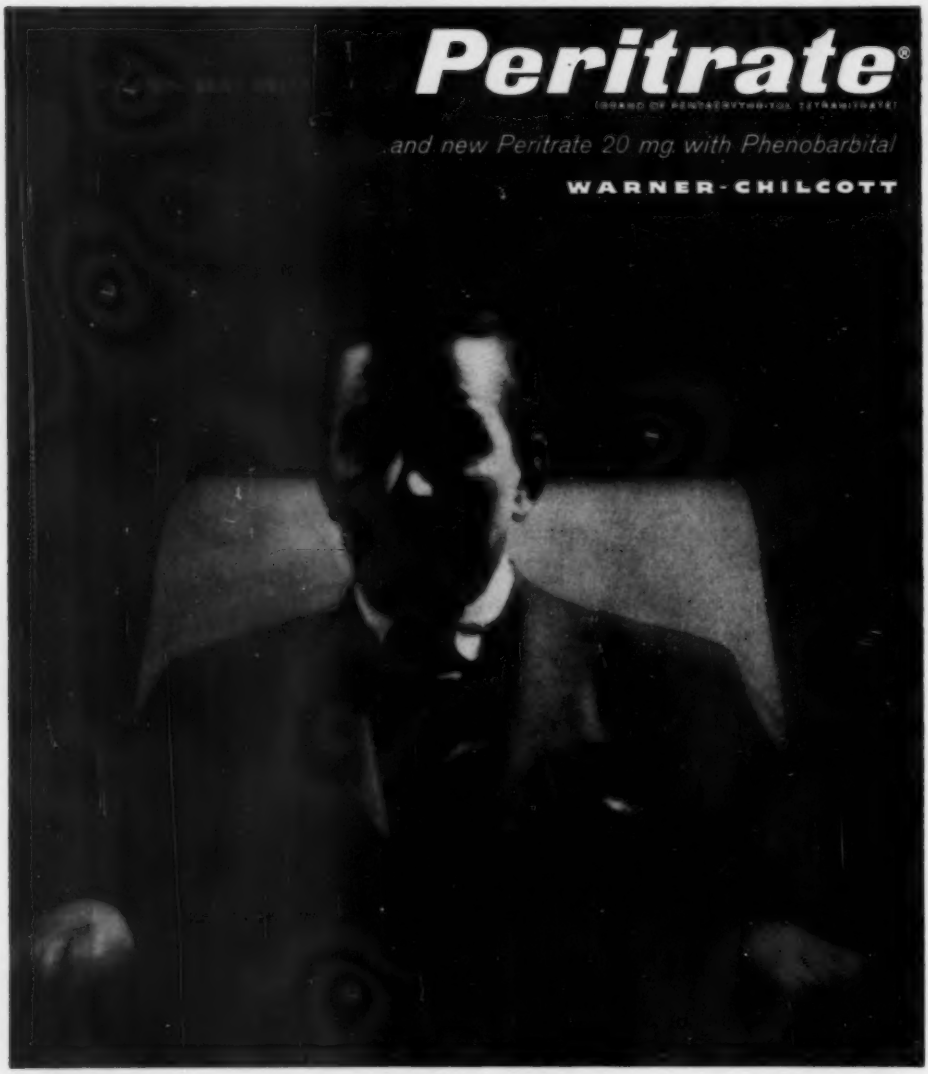

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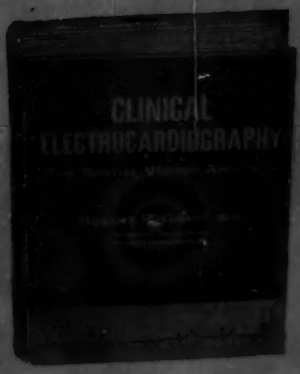

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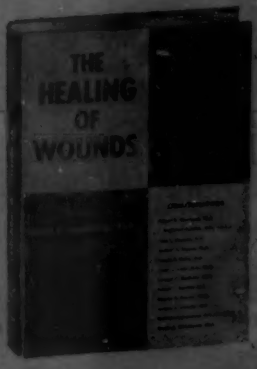

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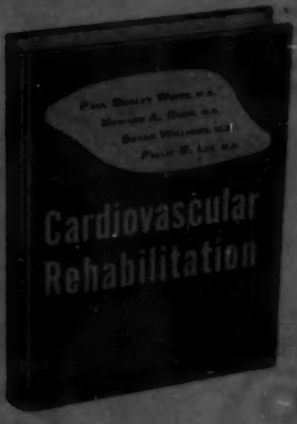

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